EFFECT OF DENERVATION AND UTERO-RENAL REFLEXES ON THE FUNCTION OF THE RABBIT KIDNEY

BY

LAURA SAURIO

HELSINKI 1957

Anal.

HELSINKI 1957
Mercatorin Kirjapaino

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PREFACE

The work for the present investigation was carried out at the Institute of Occupational Health, Helsinki.

Docent M. J. Karvonen, M.D., Ph. D., head of the Physiological Department of the Institute of Occupational Health, suggested the subject to me in the spring of 1954. I wish to thank him cordially for this, for the kind interest he has taken in my work, for the advice he has offered and for his guidance regarding the manuscript.

I am also greatly indebted to Prof. O. Eränkö, M.D., who, sparing no effort, made himself acquainted with my work, perused the manuscript and gave me valuable advice.

I am also grateful to Prof. L. Noro, M.D., Director of the Institute of Occupational Health, for the research facilities made available to me at the Institute.

I wish to thank Mr. O. Heinonen, M. Sc., for his valuable advice on planning the technique of investigation and of laboratory studies, and Mr. A. Laamanen, M. Sc., and Mr. E. Siltanen, M.Sc., for the friendly instruction given to me during the laboratory studies.

Furthermore, I wish to express my gratitude to Miss Eila Ala-Ketola and Mrs. Eva Avellan, for their technical assistance in my work.

The work was translated into English by Mrs. Hilkka Kontiopää, M. A. (Helsinki), and Mr. L. A. Keyworth, M. A. (Cantab). My sincere gratitude is due to them.

Helsinki, October 1956

L. S.

INTRODUCTION

Disturbances of water and sodium metabolism play a part in the etiology of oedematous pathological conditions.

It is known that in nephrotic oedema sodium excretion is reduced (*e.g.* Metcoff *et al.* 1954) and that sodium retention occurs in uncompensated cardiac failure (Weiser 1947, Mokotoff *et al.* 1949, Goldman and Bassett 1955). Furthermore, in the oedematous phase of glomerulonephritis the excretion of water, sodium, chlorides and potassium may decrease and in the convalescent phase, with diuresis setting in, it may rise again (*e.g.* Earle *et al.* 1951).

If the salt intake of a healthy person is low a sodium-retaining activity may sometimes, very seldom, be shown in the urine. But this activity is particularly increased in oedematous patients with nephrosis, toxaemia of late pregnancy, liver cirrhosis and cardiac failure (Deming and Luetscher 1950, Chart *et al.* 1951, Luetscher and Johnson 1954). Luetscher and Johnson attribute the retention of water and sodium to the secretion of a corticosteroid, aldosteron.

In addition to the hormonal factors, mechanical factors also may affect the development of an oedematous condition. With plasma proteins decreasing the colloid-osmotic pressure decreases, resulting in accumulation of fluid in interstitial space (Epstein 1917).

Neural factors are also known to affect the renal function, at least in some conditions.

Diversion of the bloodstream may sometimes occur in the kidneys as a result of an overstimulation of the vascular nerves. In consequence the renal cortex becomes ischaemic and the medulla hyperaemic (Trueta *et al.* 1946, Daniel *et al.* 1951, 1952). Such a diversion of the bloodstream has been produced in cat, dog, rabbit, sheep and monkey *e.g.* by electric stimulation of the renal plexus, by a rapid, severe hemorrhage, and by an adrenaline injection into

the aorta (Daniel *et al.* 1952); but intravenous injection of adrenaline failed to produce it in dog (Houck 1951).

Angiographic studies have shown that the mechanism of the diversion of the renal bloodstream, the so-called Trueta mechanism (as reported by Sophian 1953 a), is as follows. First, the calibre of the renal artery diminishes. This is accompanied by a constriction wave which starts in the distal part of the intralobular artery underneath the renal capsule. The constriction wave continues along the intralobular artery to its proximal end where it starts as a branch of the arcuate artery. Now the afferent glomerular vessels are affected, and the nearby parts of the cortex become ischaemic. In the end the only part of the cortex supplied with blood is its interior third, in which are the juxtamedullary glomeruli. From them the blood travels straight into the vasa recta and not into the peritubular vascular network as it does from the cortical glomeruli (Heggie 1947).

A diversion of the renal bloodstream in accordance with the Trueta mechanism can be produced in the rabbit *e.g.* by the utero-renal reflex, *i.e.* by distending the uterus. When the uterus of a pregnant or non-pregnant rabbit is distended the surface of the innervated kidney pales. The change in the colour of the renal surface is independent of whether the distention of the uterus is achieved by Ringer's solution, the experimental animal's own blood, the blood of another experimental animal, or mechanical means. The pallor of the renal surface may last for some time after the distension of the uterus is discontinued. The surface of a denervated kidney hardly loses any colour on distension of the uterus (Franklin 1952).

During delivery also the surface of rabbit kidney has been found to show colour changes suggestive of diversion of the bloodstream. During uterine contractions the pallor of the renal surface increases (Franklin 1952).

The supporters of the Trueta theory consider it possible that as the uterus expands the resulting increased distension and the higher tension of the uterine wall in the final weeks of pregnancy might be the etiological factor in toxaemia of late pregnancy (Sophian 1953b, Franklin 1955). If this were the case, the distension of the uterus might be expected to result in disturbed renal function, especially as regards excretion of water and electrolytes.

If the distension of the uterus does produce a cortical ischaemia in the kidneys it might be assumed that division of the splanchnic nerve, the renal vasoconstrictor, would offset the disturbed excretion resulting from distension of the uterus.

Given these circumstances, it is of interest to know whether the distension of the uterus in any way affects the excretion of water and electrolytes by the kidneys, and if so the extent of the change in the excretion. Another point to ascertain is whether division of the splanchnic nerve affects the excretion disorder possibly produced by distending the uterus.

THE PROBLEM

is, after measuring the volume of urine, to study the sodium, chloride and potassium concentration in the urine, the excretion of sodium and potassium, and the sodium: potassium concentration ratio of rabbit

(1) in the urine of the individual innervated kidneys,
(2) after division of the splanchnic nerve, in the urine of the homolateral kidney compared with that in the urine of the innervated kidney,
(3) in the urine of the individual innervated kidneys on distension of the uterus, and
(4) when both the uterus is distended and the splanchnic nerve divided, in the urine of the homolateral kidney compared with that in the urine of the innervated kidney.

REVIEW OF THE LITERATURE

RENAL FUNCTION

The excretion of water and electrolytes from the organism into the urine is governed by a complicated mechanism. The first phase of urine production, the formation of primary urine, occurs in the glomeruli. From there the urine travels to the tubules and further via collecting ducts and ureters into the bladder.

Broadly speaking, the process of urine formation can be described as follows:

1) The capsular fluid results from ultrafiltration (Richards and Walker 1930, Garby 1955). The filtration occurs through a semipermeable filter consisting of the endothelium of the glomerular capillaries and the basal membrane. It is permeable to all plasma components apart from protein and fat. The concentration of the penetrating components per volume unit is the same in the glomerular filtrate and the plasma (Walker 1930, Bayliss and Walker 1930).

2) The majority of the filtered water is reabsorbed in the proximal tubules (Richards and Walker 1935, Walker *et al.* 1941).

3) Electrolytes, mainly sodium and the corresponding anion, are also reabsorbed in the proximal tubules (Richards and Walker 1935, Walker *et al.* 1941, Ljungberg 1947) to such an extent that

4) The urine of the proximal tubules remains slightly hypotonic (Richards and Walker 1935, Smith 1951 a).

5) A considerable amount of water and electrolytes is reabsorbed in the distal tubules (Walker *et al.* 1937, Walker *et al.* 1941, Ljungberg 1947).

6) The urine turns acid or alkaline in the distal tubules (Pitts 1948, 1950).

7) Reabsorption of chlorides (Ljungberg 1947) and probably also reabsorption of water (Smith 1951b) occurs in the collecting ducts.

8) Transmission of water, sodium, chlorides and hydrogen ions has been found to occur in the ureters (Garby and Ulfendahl 1955).

9) Reabsorption of water, sodium, chlorides and potassium has also been noted in the mucosa of the bladder (Johnson *et al.* 1951, Hlad *et al.* 1956).

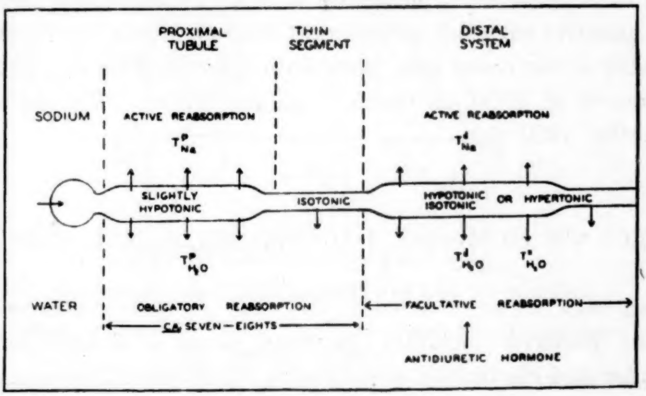

Fig. 1. — Schematic representation of sodium and water reabsorption according to Homer Smith.

Fig. 1 gives a schematic illustration of the reabsorption of sodium and water according to Smith (Smith 1951a).

The majority of the filtrated sodium is reabsorbed in the proximal tubules and a smaller part in the distal tubules (Walker *et al.* 1941, Ljungberg 1947, Smith 1951c). The amount of sodium reabsorbed in the distal tubules is roughly constant, and so is the maximal selective reabsorption of water in the distal tubules provided there is no considerable variation in the osmotic concentration of the plasma (in rabbit, Kruhøffer 1950a).

The excretion of sodium is dependent on

1) the ratio of glomerular filtration (volume of ultrafiltrate per time unit), governed by nervous and humoral factors; with the ratio declining the excretion of sodium declines (in dog, Levy and Berne 1951; in man, Chalmers *et al.* 1952; in rabbit Kruhøffer 1950b),

2) the sodium concentration of the plasma; when it increases the excretion of sodium increases without any increase in reabsorption (in rabbit, Kruhøffer 1950c), and

3) the reabsorption of sodium, governed by humoral factors.

Potassium is also reabsorbed in the proximal tubules as the potassium concentration in the urine of the proximal tubules is lower than in the plasma (in rat, Wirz and Bott 1954). The proximal tubule cells of an isolated frog's kidney can store potassium against a gradient to upwards of three times its normal concentration (Conway *et al.* 1946).

If large amounts of potassium salts are administered the potassium quantity excreted exceeds that filtered. Hence, in the tubules, probably in the distal part, potassium is secreted (in dog and man, Berliner *et al.* 1950; in man, Sirota and Kroop 1951; in rabbit, Kruhøffer 1950 d).

EFFECT OF HUMORAL FACTORS ON RENAL FUNCTION

EFFECT OF THE POSTERIOR PITUITARY HORMONE

The posterior pituitary hormone exerts a definite influence on water and electrolyte excretion by the kidney. The antidiuretic hormone of the neurohypophysis accelerates the reabsorption of water in the renal tubules and reduces the excretion of urine, which results in an increase in the chloride concentration of the urine (O'Connor 1951).

Posterior Pituitary Extract. — An intravenous injection of posterior pituitary extract produces, after a latent period of approx. 2 minutes, a decrease in diuresis, characterized by a fairly rapid but not abrupt drop and then a gradual rise (in dog, Rydin and Verney 1938, Verney 1947; in frog, Sawyer 1951; in rat, Sawyer 1952; in goat, Andersson 1955). The sodium and chloride concentration of the urine increases and, provided there is no notable change in water excretion, the excretion of sodium and chlorides also increases (in rat, Silvette 1940, Sawyer 1952; in dog, Rydin and Verney 1938, Karvonen *et al.* 1953; in man, Barclay *et al.* 1949; in goat with free access to salt, Andersson 1955). The potassium concentration of the urine and potassium excretion often increase (in rat, Sawyer 1952; in dog, Karvonen *et al.* 1953). Sometimes the potassium excretion remains unchanged in spite of an increased potassium concentration (in goat with free access to salt, Andersson 1955). The tubular chloride reabsorption obviously

WATER AND ELECTROLYTE METABOLISM IN THE GOAT. 55

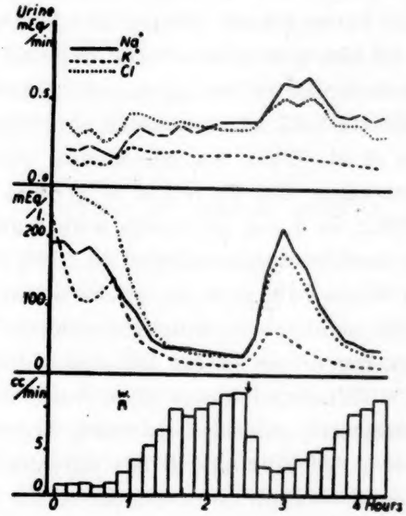

Fig. 2. (Andersson 1955). — The effect of »Pituitrin» on the water diuresis and the urinary excretion of Na, K and Cl in animal No. 2 (belonging to the saltfed group).

W: 6,000 cc of body warm water administered into the rumen through ruminal fistula.

↓: The intravenous injection of 10 milliunits of »Pituitrin».

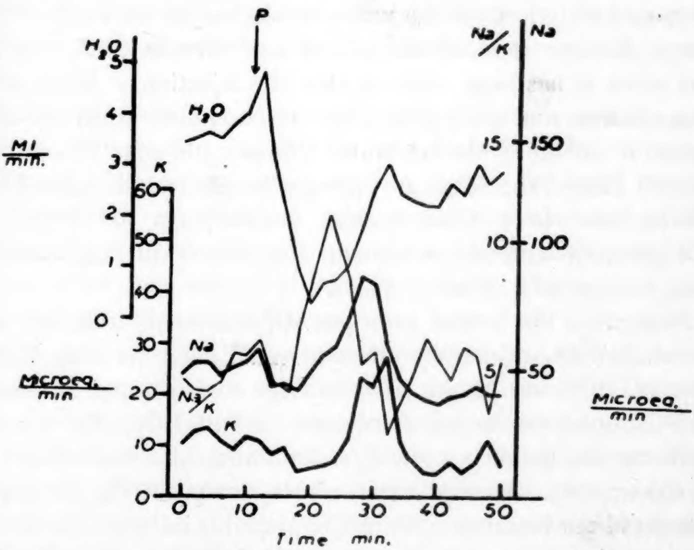

Fig. 3. (Karvonen et al., 1953). — The results of an experiment made on dog J. At the arrow P, 1.0 milliunit of pitressin was injected intravenously. When the antidiuretic response passes its maximum, the excretion of sodium and potassium increases. The ratio Na/K shows a marked rise during the antidiuretic response.

declines, resulting in increased excretion of chlorides. The glomerular filtration ratio varies (in rat, Dicker and Heller 1946).

Pitressin. — Of the principles of the extract, pitressin produces an antidiuresis similar to that produced by posterior pituitary extract (in rat, Silvette 1941; in man, Little *et al.* 1947, Ladd 1951; in dog, Karvonen *et al.* 1953). An injection of pitressin may increase the concentration and excretion of sodium and chlorides (in rat, Sawyer 1952; in 3 out of 4 dogs with diabetes insipidus, Shannon 1942; in healthy dog, Anslow *et al.* 1948, Karvonen *et al.* 1953, Anslow and Wesson 1955) or, in spite of a rise in the chloride concentration in the urine, the sodium and chloride excretion may vary, either increasing or decreasing (in man, Little et al. 1947, Nelson and Welt 1952). Small doses of pitressin may reduce the excretion of sodium and chlorides (in man, Murphy and Stead 1951). Friedman *et al.* (1956) claimed that pitressin had a diphasic effect on the sodium and water excretion of the rat; there was increased excretion and a retention phase. The potassium concentration of the urine and potassium excretion increase (in rat, Sawyer 1952; in dog, Karvonen *et al.* 1953, Anslow *et al.* 1948, Anslow and Wesson 1955). Used on a hydropenic dog, whose water excretion from the kidneys is low, pitressin does not seem to have any consistent effect on the water or electrolyte excretion of the kidneys (Anslow *et al.* 1948, Anslow and Wesson 1955). On the other hand, it has been claimed that the injection of pitressin increases sodium and often potassium excretion more when the urine volume is low than during water diuresis (in dog, Brooks and Pickford 1956). The effect of pitressin on electrolyte excretion is probably due to reduced tubular reabsorption of electrolytes while glomerular filtration remains unchanged (in dog, Shannon 1942, Anslow and Wesson 1955).

Pitocin. — The second principle of posterior pituitary extract, pitocin, has no antidiuretic effect in small doses (in dog, Karvonen *et al.* 1953) but has an effect in large doses (in dog, Abrahams and Pickford 1954; in rat, Berde and Cerletti 1956). An injection of pitocin may produce a rise in sodium and chloride excretion (in rat, Fraser 1942, Dicker and Heller 1946, Sawyer 1952), but mostly it has not been found to exert any appreciable influence on electrolyte excretion (in dog, Anslow *et al.* 1948, Karvonen *et al.* 1953, Anslow and Wesson 1955). The rise possibly produced by pitocin in

the excretion of electrolytes was attributed by Dicker and Heller to reduced chloride reabsorption, by Anslow and Wesson to the small amount of the antidiuretic principle contained in the pitocin fraction. Pure oxytocin has no appreciable effect on the excretion of sodium and potassium (Brooks and Pickford 1956).

EFFECT OF CERTAIN STIMULI

Hypothalamus. — Andersson and MacCann (1955) produced antidiuresis of the neurohypophyseal type in the goat by electric stimulation of the paraventricular nucleus, the supraoptic nucleus of the hypothalmus, or the supraoptico-hypophyseal tract. The urine concentration of sodium and chlorides and sodium and chloride excretion increased. The urine potassium concentration also increased, but there was no regular rise in potassium excretion. The glomerular filtration ratio showed no appreciable change. Hence the stimulation of the hypothalamus produced in the renal excretion a change similar to that produced by the pituitary antidiuretic hormone. Electric stimulation of the midbrain produced in the innervated kidney an immediate antidiuresis which ended after the stimulus was removed. In a denervated kidney the antidiuresis was produced 2—3 min. after application of the stimulus and lasted up to 20 minutes after the simulus was removed (in cat, Koella 1949).

Emotional Stress. — Pain and emotional stress usually produce antidiuresis (in dog, Rydin and Verney 1938, O'Connor and Verney 1942, Verney 1947; in man, Mirsky and Stein 1953; in dog, Abrahams and Pickford 1954). Antidiuresis induced by the stimulus of pain is similar to that obtained by injecting the pituitary posterior lobe extract (Rydin and Verney 1938). If the pituitary stalk is destroyed or the posterior lobe of the hypophysis is removed, pain stimulus produces no antidiuresis (in rabbit, Haterius 1940) or approx. 5 per cent antidiuresis (in dog, O'Connor and Verney 1942). Pain stimulus applied to dog lowered the glomerular filtration ratio and the renal sodium excretion (Surtshin *et al.* 1952, Berne 1952) and reduced the renal plasma flow (Berne 1952). According to Rydin and Verney (1938) and Verney (1946), emotional stress produces in dog a rise in the urine chloride concentration. Hence pain stimulus seems to affect the glomerular and tubular urine formation mechanism.

Exercise. — Exercise may also produce antidiuresis (in dog, Klisiecki *et al.* 1933b, Rydin and Verney 1938; in man, Covian and Rehberg 1937, Barclay *et al.* 1947). As a result of exercise, the chloride excretion, glomerular filtration ratio and renal plasma flow of man may decrease (Barclay *et al.* 1947).

EFFECT OF THE ADRENAL

Adrenaline. — In small doses, adrenaline produces a transient antidiuresis that starts very suddenly (in dog, Theobald and Verney 1935, Verney 1947, Pickford and Watt 1951). With dog, larger doses, 0.04—0.2 mg, give a diphasic antidiuresis; a transient antidiuresis sets in first, followed by an intermediate rise in urine flow and then by another antidiuresis of longer duration, possibly produced by the antidiuretic hormone of the pituitary (Eränkö and Karvonen 1952a). Antidiuretic activity in the urine can be shown during the latter antidiuresis by the reinjection of urine (Eränkö and Karvonen 1952b). Doses of 0.5 mg or more produce a monophasic or diphasic antidiuresis (in dog, Eränkö and Karvonen 1952b). When the posterior lobe of the pituitary is removed the longer antidiuresis disappears (Dearborn and Lasagna 1952).

Adrenaline reduces sodium and chloride excretion in most cases (in dog, Arnstein and Redlich 1923, Blake 1951, Kaplan *et al.* 1952; in man, Jacobson *et al.* 1951, Smythe *et al.* 1952, Nickel *et al.* 1954). Potassium excretion decreases (in man, Duncan *et al.* 1951, Jacobson *et al.* 1951, Smythe *et al.* 1952, Nickel *et al.* 1954). The urine sodium: potassium ratio increases (Eränkö *et al.* 1953). The adrenaline-induced drop in electrolyte excretion is probably explicable from the fact that glomerular filtration declines and the renal blood flow is retarded (in dog, Pickford and Watt 1951, Kaplan *et al.* 1952, Moyer and Handley 1952; in man, Jacobson *et al.* 1951). However, Smythe *et al.* (1952) found that the human glomerular filtration ratio remained roughly unchanged and attributed the drop in electrolyte excretion to increased tubular reabsorption.

Adrenocortical Hormones. — Luetscher and Johnson (1954) showed that the sodium-retaining activity in the urine of oedematous patients with nephrosis, cardiac failure and liver cirrhosis was due to the secretion of a corticosteroid, aldosteron.

Renzi *et al.* (1956) used slightly hydrated, adrenalectomized

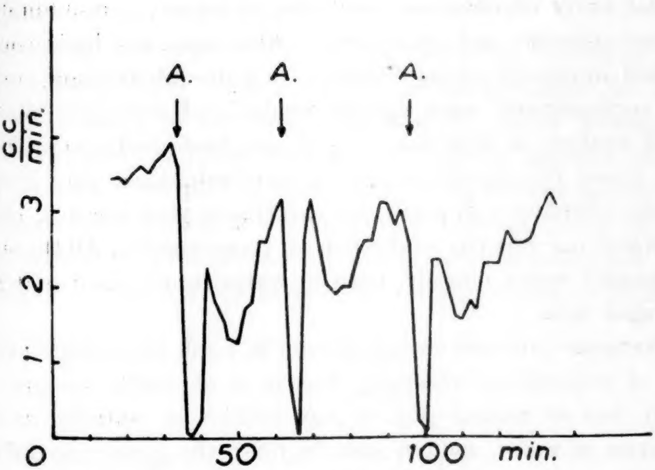

Fig. 4. (Eränkö and Karvonen 1952a). — Effect of successive equal doses of adrenaline on urine flow. »Jesse» on Pavlov stand (9th Oct., 1951). A., 0.5 mg adrenaline intravenously.

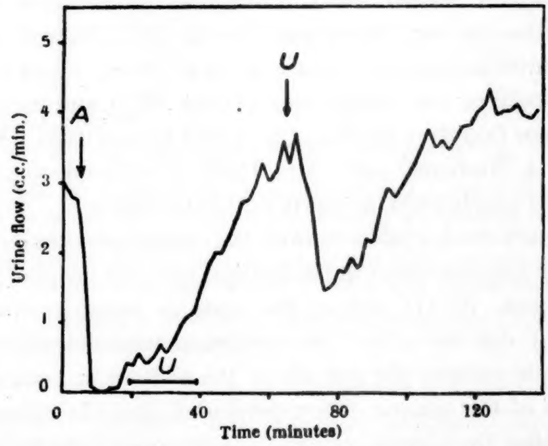

Fig. 5. (Eränkö and Karvonen 1952b). — Water-diuresis curve from the bitch 'Diogenes', in a Pavlov stand. At $A\downarrow$, 0.5 mg. adrenaline was injected intravenously.Urine was collected at U —, and re-injected at $U\downarrow$.

rats to study the effect of aldosteron and other steroids on experimental water intoxication, creatinine clearance, para-aminohippuric acid clearance and urine volume. Aldosteron and hydrocortisone showed an equally strong resistance to water intoxication; cortisone and corticosterone were slightly weaker, and desoxycorticosterone much weaker. In high doses aldosteron, hydrocortisone and cortisone raised the creatinine and para-aminohippuric acid clearance equally effectively; in lower doses, cortisone was inactive. Desoxycorticosterone was the weakest in all these respects. All the steroids accelerated water diuresis, both in water intoxication and in the clearance tests.

Cortisone produces in man a drop in water excretion and retention of sodium and chlorides (Perera *et al.* 1949, Sprague *et al.* 1950), but in normal dog it may induce an initially increased excretion of water, sodium and chlorides, the glomerular filtration ratio may increase transiently (Davis and Howell 1953). The potassium excretion increases (Davis and Howell 1953, Roberts and Pitts 1953, Bass and Houck 1953).

Desoxycorticosterone may induce increased water excretion in dog (Davis and Howell 1953), a drop in the excretion of sodium and chlorides (in dog, Davis and Howell 1953, Howell and Davis 1954; in adrenalectomized mouse in large doses, Forsyth 1953; in adrenalectomized rat, Singer and Vennig 1953) and usually a rise in potassium excretion (in dog, Davis and Howell 1953, Howell and Davis 1954, Roberts and Pitts 1953; in adrenalectomized dog, Howell and Davis 1954, Roberts and Pitts 1953).

Woodbury *et al.* (1950) showed that desoxycorticosterone raised the sodium concentration in the plasma and reduced the potassium concentration, ACTH raised the sodium concentration of the plasma but did not affect the potassium concentration, adrenocorticotropic extract did not affect the sodium or potassium concentration of the plasma. They concluded that the adrenal cortex can normalize the plasma sodium concentration however much it is disturbed. This may be either via the direct effect on the cells of the renal tubules or by inhibition of the secretion of ACTH.

EFFECT OF NERVOUS FACTORS ON RENAL FUNCTION

The volume of urine excreted by the individual innervated kidneys sometimes varies. Verney (1930) collected separately the urine from the kidneys of an unanaesthetized dog using permanent, transvesical ureteral catheters. He found that the kidneys usually excreted equal quantities of urine, but the quantities excreted in the experimental period of one hour were different; when the difference was at its greatest the left kidney excreted 0.8 cc./min. and the right 0.17 cc./min. Subsequently, the quantities excreted by

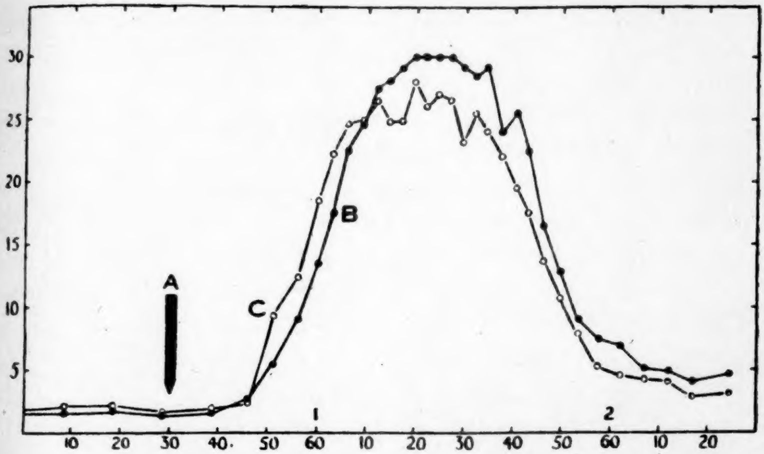

Fig. 6. (Klisiecki et al., 1933a). — Response of right and left kidneys to the introduction of water into the stomach. Ureters extended to the exterior by the method described in the text. At A 250 c.c. tap water at a temperature of 30° C. were given by stomach-tube. B and C are the rates of collection of urine from the right and left kidney respectively.

Ordinate = rate of flow of urine in cubic centimetres per 15 minutes.
Abscissa = time in minutes and hours.

each kidney were the same. Klisiecki *et al.* (1933a) found similarly, with dog, that the urine volume of the individual kidneys was often different. In consecutive test periods either the left or the right kidney excreted more urine. The variation was especially noticeable when the urine volume was small.

Nervous factors have long been known to be capable of affecting the renal function. Bernard (1859), after unilateral severing of the splanchnic nerve of dog, found that the measure had an

increasing effect on the excretion of urine. Many authors have since studied the effect of the denervation of kidney on the excretion of urine; the results show some lack of correspondence.

Vasomotoric fibres with a much stronger vasoconstrictive than vasodilative effect enter the kidneys with the splanchnic nerve (Bradford 1889, Milliken and Karr 1925, Gruber 1933). It is known that division of the splanchnic nerve increases the renal blood flow of anaesthetized dog (Burton-Opitz and Lucas 1908). In addition, it has been found that the splanchnic nerve only innervates the homolateral kidney (Bradford 1889, Burton-Opitz and Lucas 1909). Brull *et al.* (1955) found that renal denervation of the anaesthetized dog eliminates totally or partially vasoconstriction of the renal arteries which occurs in response to a rise of pressure and prevents variations of the blood flow.

Methods of Kidney Denervation. — The splanchnic nerve was severed by Bernard (1859), Jungmann and Meyer (1913), Marshall and Kolls (1919), Kaplan and Rapoport (1951) and Kaplan *et al.* (1951). The nerves around the renal artery and vein were severed by Klisiecki *et al.* (1933a), Rhoads *et al.* (1934), Theobald and Verney (1935), Berne (1952), Berne and Levy (1952), and Boylan *et al.* (1953). Rydin and Verney (1938) severed the renal nerves and decentralized the whole abdominal sympathicus system, removing the ganglions from the second lumbar to the first sacral. Hiatt (1942) severed the splanchnic nerve and, in addition, performed a sympathicus section either from the thoracic region or from below the diaphragm to the second lumbar ganglion. Kriss *et al.* (1948) performed supradiaphragmatic splanchnicus resection and usually also sympathectomy at the spot where the sympathicus trunk passes through the diaphragm. Surtshin *et al.* (1952) made a splanchnicus section by a thoracoabdominal operation, removing the sympathicus trunk from the eighth or tenth-eleventh thoracic to second or third lumbar ganglion, in addition to which the adventitia of the renal artery was freed from innervation.

EFFECT OF DENERVATION ON RENAL EXCRETION

The urine flow of a denervated kidney is greater than that of the innervated kidney in anaesthetized rabbit (Jungmann and

Meyer 1913) and anaesthetized dog (Bernard 1859, Marshall and Kolls 1919, Kriss *et al.* 1948). The urine chloride concentration and chloride excretion of a denervated kidney are higher in anaesthetized rabbit (Jungmann and Meyer 1913) and anaesthetized dog (Marshall and Kolls 1919, Kriss *et al.* 1948, Kaplan *et al.* 1951, Kaplan and Rapoport 1951). The urine sodium concentration of a denervated kidney is also higher (Kaplan *et al.* 1951) and the sodium excretion higher in anaesthetized dog (Kaplan and Rapoport 1951, Berne 1952, Sartorius and Burlington 1956); in addition, potassium concentration and potassium excretion are higher on the denervated side of anaesthetized dog (Kaplan and Rapoport 1951).

With a conscious dog the urine flow of the denervated and innervated kidney are equal (Bykow and Alexejew-Berkmann 1931, Klisiecki *et al.* 1933a, Hiatt 1942, Surtshin *et al.* 1952, Boylan *et al.* 1953), the chloride excretion equal (Klisiecki *et al.* 1933a) and sodium excretion equal (Berne 1952, Boylan *et al.* 1953), and also the potassium excretion equal (Surtshin *et al.* 1952).

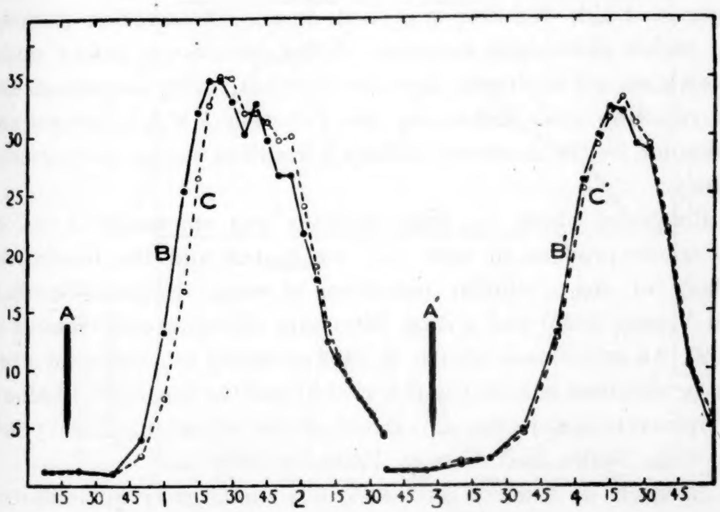

Fig. 7. (Klisiecki et al. 1933a). — Dog. No. 37. The responses of the kidneys to the giving of water after section of the left splanchnic nerves. Nerves divided May 14, 1930. B = response of right kidney, C = that of left, on May 16, 1930. At A 280 c.c. water were given by stomach tube. The responses were again obtained on May 20, 1930, and are shown at B′ and C′, 300 c.c. being given at A′. Abscissa = time in minutes and hours. Ordinate = rate of urinary flow in cubic centimetres per 15 minutes.

The glomerular filtration ratio and renal plasma flow of anaesthetized dog is greater on the denervated side (Berne 1952); unanaesthetized dog shows no essential difference (Hiatt 1942, Berne 1952). Rhoads *et al.* (1934), however, found that novocaine anaesthesia of the renal nerves or surgical denervation of the kidney of dog exerted no uniform influence on urea clearance or renal blood flow in investigations made, apparently, under anaesthesia.

EXCRETION OF THE DENERVATED KIDNEY IN CERTAIN CONDITIONS

Anaesthesia. — Deep ether or cyclopropane anaesthesia reduces the urine volume, glomerular filtration ratio and renal blood flow of innervated kidneys of dog (Craig *et al.* 1945). Miles and de Wardener (1952) showed that inhalation of ether and cyclopropane produced vasoconstriction in the innervated dog kidney; in denervated kidney the vasoconstriction was small and highly transient or non-existent. Surtshin *et al.* (1952) found that, under deep ether and pentobarbital anaesthesia, the sodium and potassium excretion of an innervated dog kidney decreased; on the denervated side the drop was small or nil. »Denervation diuresis» and higher electrolyte excretion of the denervated kidney under anaesthesia are explicable from the fact that, under anaesthesia and the resulting vasoconstriction, the excretion of water, sodium and potassium by the innervated kidney is less than that by a denervated kidney.

Emotional Stress. — Pain stimulus and emotional stress on the whole produce in both the denervated and the innervated kidney of dog a similar inhibition of water diuresis (Theobald and Verney 1935) and a drop in sodium excretion (Surtshin *et al.* 1952). An antidiuresis similar to that produced by emotional stress can be obtained in both the denervated and the innervated kidneys by intravenous injection of extract of the posterior pituitary lobe (in dog, Rydin and Verney 1938).

Exercise. — Exercise produces in a similar way an inhibition of the water diuresis of the denervated and innervated kidney (Klisiecki *et al.* 1933b).

Asphyxia. — In anaesthetized rabbit, asphyxia leads to paling of the innervated kidney surface and antidiuresis; the surface of the denervated kidney does not turn pale, nor is antidiuresis a

regular finding. Bilateral adrenalectomy does not reduce the renal changes due to asphyxia (Franklin *et al.* 1951).

Lowered Cardiac Output. — When the cardiac output of anaesthetized dog is artificially lowered the water excretion, glomerular filtration ratio, renal blood flow and sodium excretion of the denervated and innervated kidney are equal (Berne 1951, Berne and Levy 1952).

CONNECTIONS BETWEEN UTERUS AND KIDNEY

Utero-renal Reflex. — As was pointed out in the introduction, a diversion in the bloodstream of rabbit kidney can be produced *e.g.* by distending the uterus. The pallor of the renal surface has no connection with the method of distending the uterus.

Franklin and Winstone (1955) report that distension of the uterus results in the following phenomena: 1) Reflex renal-cortical

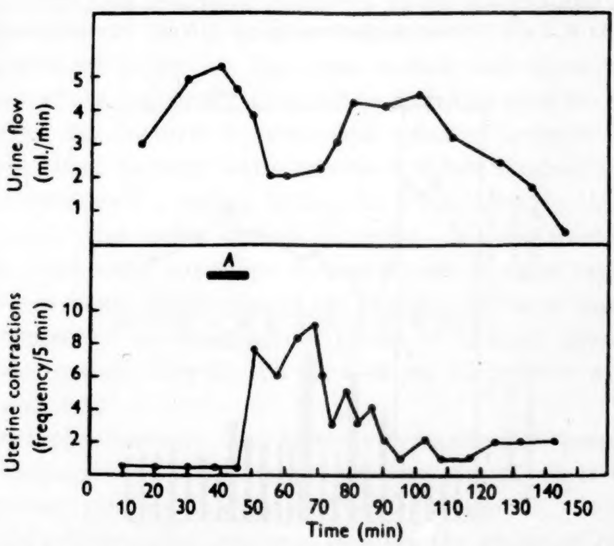

Fig. 8. (Abrahams and Pickford 1954). — Effect of emotion on urine flow and uterine motility. Angela, 16 Apr. 1953. Upper record, urine flow. Lower record, frequency of uterine contraction. At zero time 300 ml. water by mouth. During period *A* preparations were made for an intracarotid injection which was not given.

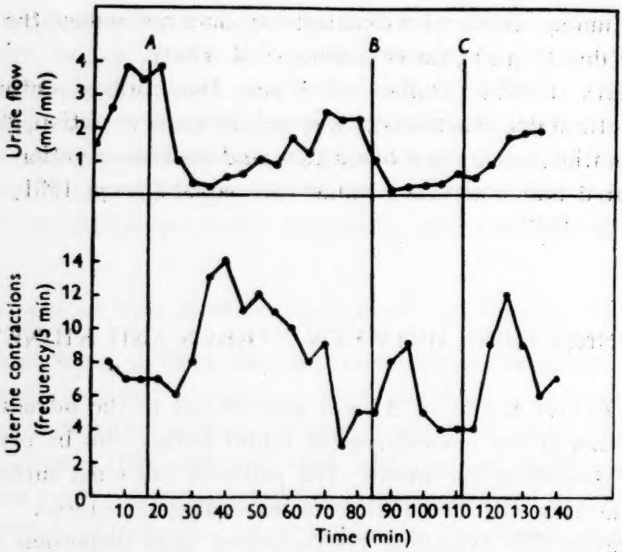

Fig. 9. (Abrahams and Pickford 1954). — Effect of intracarotid injection of NaCl on urine flow and uterine motility. Lady, 23 Apr. 1953. Upper record, urine flow. Lower record, frequency of uterine contraction. At zero time 350 ml. water by mouth. At *A*, 2.4 ml. 1.7 M-NaCl solution by intracarotid injection in 5 sec. At *B*, 5 mU Pitressin intravenously. At *C*, 5 mU Pitocin intravenously.

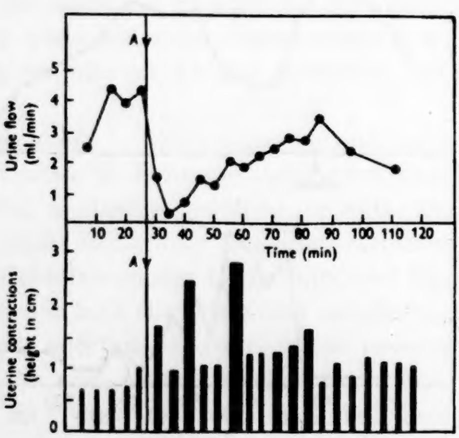

Fig. 10. (Abrahams and Pickford 1954). — Effect of intravenous Pitocin on urine flow and uterine motility. Lady, 12 May 1953. Upper record, urine flow. Lower record, frequency of uterine contraction. At zero time 350 ml. water by mouth. At *A*, 100 mU Pitocin intravenously.

ischaemia which follows immediately on distension, its degree depending on the amount of distension. It fails to appear when the innervation of the kidney is severed. 2) Cortical ischaemia produced by the adrenal, which sets in slightly later and lasts longer than the distension. It fails to appear when the effect of the adrenal is excluded. 3) Distension of the cornu uteri causes a rise in arterial pressure. In addition, Franklin and Winstone concluded: it is possible that the increased resistance of the uterine muscle has a reflex effect on the hypophysis.

Uterus and Hypophysis. — Ferguson (1941) found that electric stimulation of the pituitary stalk of rabbit and cat liberates oxytocin. Distension of the cervix of rabbit also liberates oxytocin, increasing uterine motility. A similar effect is obtained from distension of the uterine cornu, but not with equal regularity.

Abrahams and Pickford (1954) showed that in dog emotional stress and intravenous injection of hypertonic NaCl inhibits water diuresis and simultaneously increases uterine motility. An injection of <5 mU of pitressin or a 15—20-fold dose of oxytocin produced an effect on the water excretion of the kidneys and uterine motility similar to that of emotional stress.

Vagino-renal Reflex. — The renal surface also turns pale on distension of the vagina (Franklin 1955). Franklin used the vagino-renal reflex to stimulate a utero-renal reflex in order to observe the above effect on renal water excretion. When a rabbit's vagina was distended with a rubber balloon to a size equal to the foetal volume, the renal cortex turned ischaemic. On continued distension the renal water excretion decreased, and in some cases proteinuria was noted. Distension of the rabbit's vagina to equal the foetal volume for an experimental period of 14 days reduced the renal water excretion by 31—52 per cent per kilogramme of body-weight and day.

5-hydroxytryptamine. — 5-hydroxytryptamine is present in various organs, *e.g.* in the central nervous system. It is known to affect both uterine motility and renal function.

5-hydroxytryptamine contracts strongly the uterus of rat (*e.g.* Costa 1956) and reduces diuresis at least in dog and rat. Erspamer and Ottolenghi (1953) found that 5-hydroxytryptamine retarded the blood flow of the glomeruli and peritubular capillaries of the rat. Page (1952) showed that 5-hydroxytryptamine contracted

the blood vessels of dog kidney. In man, 5-hydroxytryptamine may result in a considerable sodium retention (Hulet and Perera 1956).

Reid (1952), working with cat, reported that 5-hydroxytryptamine at first caused a drop in arterial pressure, then a rise and subsequently a drop of longer duration. He assumed that the substance had a stimulating effect on the adrenal medulla.

PRESENT INVESTIGATION

OPERATIONS

A total of 14 rabbits was employed in the experiments; for the purpose, they were operated on by the methods described in the following.

Anaesthesia. — The basic anaesthetic was nembutal (sodium pentobarbital, 60—300 mg) administered intravenously. If required, ether was also given.

Denervation of the Left Kidney (*a.m.* Krause). — A median incision, length approx. 8—10 cm, was made along the linea alba of the abdomen distally from the processus ensiformis, and the peritoneum was exposed. The stomach and the intestines were pushed to the right and covered in a cloth dipped in warm physiological saline. An incision was made in the posterior peritoneum. The left splanchnic nerve was exposed at the pars lumbalis of the diaphragm or where it passes by the caudal edge of the pars lumbalis into the abdominal cavity. The left splanchnic nerve was divided and an approx. 0.5—1.0 cm long piece resected and preserved. The stomach and the intestines were pushed back into the abdominal cavity. The peritoneum and the abdomen were closed layer by layer with catgut, and the skin sewn with silk sutures. The right kidney was left intact for comparison of the excretion of a denervated and an innervated kidney. The left splanchnic nerve of 8 rabbits was divided. A histological specimen was made of the piece resected at the operation, to make sure that it was nerve tissue.

Transplantation of Ureters (Markowitz 1949a). — The bladder was exposed by a median incision in the caudal part of the abdomen, opened, and the major part of it resected. The ureteral orifices were transplanted by introducing pieces of bladder, approx. $^3/_4$ cm

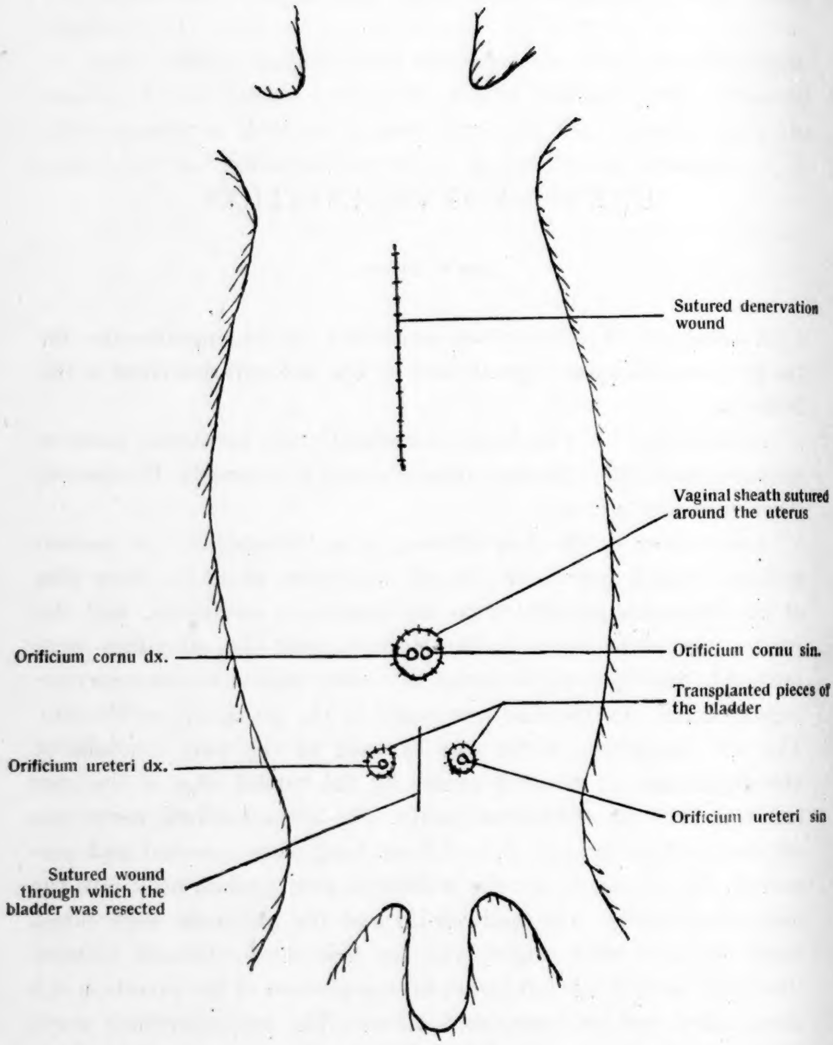

Fig. 11. — Schematic picture illustrating the anatomic conditions of an operated rabbit.

in diameter, with a ureteral orifice in the middle, through openings made in the muscular layer and skin on both sides of the median line and enlarged by a blunt instrument. The small bladder pieces were sutured into wounds in the skin by interrupted sutures of thin catgut. The wound in the median line was closed with interrupted catgut sutures. In this way the left ureteral orifice was located on the left of the median line and the right ureteral orifice to the right of it. The urine excreted by each of the kidneys could be collected separately. The ureteral orifices of all the rabbits employed in the experiments were transplanted.

Exteriorization of the Uterus (Markowitz 1949b). — Entry was again made into the abdominal cavity via a median incision, orally of the transplanted ureteral orifices. The uterus was raised. The vagina was severed approximately 1.5 cm caudally of the uterus. The caudal part of the vaginal was closed by a few catgut sutures and left in the abdominal cavity. The proximal part of the vagina was sutured ring-like around the uterus by interrupted sutures which penetrated the peritoneum, muscular layer, fascia and skin. Usually catgut sutures only were used, sometimes additionally a few silk sutures. After the exteriorization of the uterus the orifices of the uterine cornua were visible on both sides of the median line, and the uterus could be experimentally distended at will. The uterus of 11 rabbits was exteriorized.

Post-operative Treatment. — The operated rabbits were given various courses of antibiotics as required. The wounds were cleaned daily, treated with ointments and bandaged. Occasional inversions of the uterus were repositioned. If necessary, the rabbits were given infusions of saline, glucose or amino acids, and vitamins. The silk sutures were removed after 8—12 days. The experiments were begun some 8—12 days after the operation, when the wounds had healed. The operated rabbits lived for or were sacrificed some 1—3 months after the operation. When the denervation of the kidney was effected by a second, separate operation the major part of the rabbits died of respiratory difficulties after the second operation. As a rule the rabbits operated on lived longer the more careful the treatment accorded to them.

EXPERIMENTAL ANIMALS

R a b b i t I. Weight 2,400 g. Exteriorization of the uterus was performed March 10, 1955. The bladder was resected, and the ureteral orifices transplanted to the abdominal surface. Division of the left splanchnic nerve was attempted but the histological preparation was not nerve tissue. The left splanchnic nerve was divided April 7, 1955, at the pars lumbalis of the diaphragm. A piece 0.5 cm in length was removed and found histologically to be nerve tissue. The rabbit died April 18, 1955. No differences were seen between the right and left kidneys and adrenals from histological preparations.

R a b b i t I I. Weight 2,700 g. Exteriorization of the uterus was performed November 15, 1954. The bladder was resected and the ureteral orifices were transplanted to the abdominal surface. The rabbit was killed Dec. 15, 1954, because one of the ureters was blocked.

R a b b i t I I I. Weight 2,700 g. Exteriorization of the uterus was performed Dec. 11, 1954. The bladder was resected and the ureteral orifices transplanted to the abdominal surface. The left splanchnic nerve was divided Dec. 22, 1954. The rabbit died after the second operation. No experiments were made after denervation.

R a b b i t I V. Weight 2,500 g. Exteriorization of the uterus was performed Dec. 29, 1954. The bladder was resected and the ureteral orifices were transplanted to the abdominal surface. The left splanchnic nerve was divided on Jan. 8, 1955. The rabbit died after the second operation. No experiments were made after denervation.

R a b b i t V. Weight 2,400 g. Exteriorization of the uterus was performed March 13, 1955. The bladder was resected and the ureteral orifices transplanted to the abdominal surface. The left splanchnic nerve was divided April 7, 1955. The rabbit died after the second operation. No experiments were made after denervation.

R a b b i t V I. Weight 2,850 g. Exteriorization of the uterus was performed Oct. 20, 1954. The bladder was resected and the ureteral orifices transplanted to the abdominal surface Nov. 3, 1954. The rabbit was killed Nov. 19, 1954, because of symptoms of labyrinthine irritation.

R a b b i t V I I. Weight 2,200 g. The left splanchnic nerve was divided Sept. 15, 1954, at the pars lumbalis of the diaphragm. The

bladder was resected and the ureteral orifices transplanted to the abdominal surface. The rabbit was killed Oct. 30, 1954. No difference was seen between the two kidneys and adrenals from histological preparations.

Rabbit VIII. Weight 2,350 g. The left splanchnic nerve was divided April 1, 1954, at the pars lumbalis of the diaphragm. The bladder was resected and the ureteral orifices transplanted to the abdominal surface. The uterus was exteriorized. The blood circulation of the uterus was damaged during the operation and resulted in uterine necrosis. However, the site of exteriorization of the uterus healed gradually. The rabbit was killed May 25, 1954.

Rabbit IX. Weight 1,900 g. The left splanchnic nerve was divided April 5, 1954, caudally of the pars lumbalis of the diaphragm. The uterus was exteriorized. The bladder was resected and the trigonum vesicae urinariae was exteriorized to the abdominal surface. The rabbit died April 30, 1954.

Rabbit X. Weight 2,580 g. The splanchnic nerve was divided April 21, 1955, caudally of the pars lumbalis of the diaphragm. The uterus was exteriorized, the bladder resected and the ureteral orifices transplanted to the abdominal surface. The rabbit died July 30, 1955. Autopsy gave no special findings.

Rabbit XI. Weight 2,950 g. The left splanchnic nerve was divided April 23, 1955, at the pars lumbalis of the diaphragm. The uterus was exteriorized, the bladder resected and the ureteral orifices transplanted to the abdominal surface. The rabbit died July 19, 1955.

Rabbit XII. Weight 2,400 g. The left splanchnic nerve was divided Feb. 3, 1955, caudally of the pars lumbalis of the diaphragm. The uterus was exteriorized, the bladder resected and the ureteral orifices transplanted to the abdominal surface. The exteriorized uterus opening was so constricted that the orifices of the uterine cornua were not visible. A second operation was performed Feb. 10, 1955, to enlarge the exteriorized uterus opening. The result was good. The rabbit was killed March 25, 1955.

Rabbit XIII. Weight 2,200 g. The left splanchnic nerve was divided Sept. 27, 1954, caudally of the pars lumbalis of the diaphragm. The bladder was resected and the ureteral orifices transplanted to the abdominal surface. The rabbit was killed Oct. 15, 1954, because of symptoms of labyrinthine irritation.

R a b b i t X I V. Weight 2,250 g. The uterus was exteriorized March 17, 1954, the bladder resected and the trigonum vesicae urinariae was exteriorized to the abdominal surface. A corrective operation was performed April 7, 1954, to transplant the poorly visible ureteral orifices to the abdominal surface by a second resection of a part of the bladder. The rabbit died May 8, 1954.

In addition to the experimental animals listed above, there were two rabbits that recovered well from splanchnicotomy, exteriorization of the uterus and transplantation of the ureteral orifices, but contracted complications before any experiments could be effected.

TECHNIQUE OF THE EXPERIMENTS

Preparation for the experiment. — In the early stage of the investigations the rabbits were made to fast the night before the test; they were allowed to drink water ad libitum. But the fast seemed to constitute a strain for them. As the primary purpose of the investigation was to compare the excretion of the individual kidneys, almost all the tests were made with rabbits which were allowed to drink water ad libitum and eat their usual food before the test started.

Experimental Conditions. — The experiments were not started until the animals had recovered from the operation. None of the animals were anaesthetized for the experiments. The experiments were carried out in a quiet room with a stable temperature (+20°C).

Development of Diuresis. — A continuous infusion of 0.45 per cent saline was made into the auricular vein, approx. 8—35 drops per minute, to produce and ensure a constant excretion of urine. The drip rate was correlated with the urine flow. In some tests, when intravenous infusion failed, water at room temperature was introduced into the stomach by a thin polyethylene tube, to start with approx. 30 cc. per kilogram of bodyweight twice at an interval of 1—1.5 hours and later, with the experiment continuing, 10—40 cc. every ½—1 hour depending on the urine flow.

Collection of Urine. — The experimental animal was kept in position in a stand made for the purpose. The urine was collected

separately from both ureters via small funnels into graded tubes. The funnels were made so that they could be placed under the ureteral orifices and kept tightly pressed against the abdominal surface either by hand or by holder. The urine volume of each 5 min. was read off directly from the graded tubes and stored for study. Ureteral catheters proved unsuitable. In the course of time they caused haemorrhages in the urinary tract, which raised the sodium concentration of the urine.

Distension of the Uterus. — To effect the distension, a small balloon was made of thin, elastic rubber; its diameter, collapsed, was approx. 4 mm. A thin polyethylene tube was connected with the balloon. The distension was effected at as stable a phase of urine excretion as possible. At the beginning of the distension, the balloon was introduced, collapsed, by means of a probe into one of the uterine cornua and filled immediately by an injection via the polyethylene tube of a certain volume (2—10 cc.) of warm water (temperature +37°C) in the course of 45 sec. — 5 min. The distension was continued for 10 min. — 2 hours, during which the rubber balloon was kept filled by wedging the piston mechanism of the syringe. After the distension was discontinued, the balloon was first emptied and then immediately removed from the uterine cornu. Urine excretion observations were continued by measuring the volumes every 5 minutes and storing the samples, until the excretion of urine again was stable.

Introduction of the collapsed rubber balloon into the uterine cornu did not seem to disturb the rabbit, nor did the fairly loose and soft tissue of the uterine cornu offer much resistance. When the distension process was started the rabbit kept quiet and did not kick. But with the process in progress the rabbit emitted weak sounds from which it could be concluded that the animal felt some pain. As the distension continued the feeling of pain seemed to pass over. On cessation, when the balloon was emptied, the rabbit again seemed to experience a disagreeable sensation, presumably pain, which again passed over in a moment. The rabbit's reactions to the distension of the uterus depended on the rate and volume of the distension; they were more marked the greater the distension introduced.

Duration of the Experiments. — From the start of the infusion of 0.45 per cent NaCl it was 1.5—5 hours, depending on the indi-

vidual animal, before a sufficiently high and stable diuresis developed. When water was given by the stomach tube the diuresis came earlier but was not so stable as that obtained by continuous saline infusion. The duration of the whole experiment varied from 5—12 hours.

LABORATORY INVESTIGATIONS

Excretion of Urine. — The urine excretion per time unit (cc./min). was computed from the urine volumes measured and the time taken to excrete them.

Sodium and Potassium Determination

The sodium and potassium was determined from the urine sample by a flame photometer with lithium as the internal standard. The flame photometer employed was that constructed by Karvonen and Laamanen (1952). By this method, the colour intensity of the flame of suitable sodium and potassium dilutions studied is measured by means of photoelectric cells as a galvanometric deviation and compared with the colour intensity of known sodium and potassium dilutions.

Sodium and Potassium Concentration. — The sodium and potassium concentrations (mEq./l., 1.0 mEq./l. = molecular weight mg./l.) were computed by determining the galvanometric deviations of control solutions and comparing them with deviations of known dilutions of the urine specimens.

Sodium and Potassium Excretion. The excretion of sodium and potassium per time unit (microeq., 1.0 microeq./min. = molecular weight mg./min.) was computed from the known excretion of urine and the sodium and potassium concentrations determined by the flame photometer.

Sodium: Potassium Ratio. — The sodium: potassium ratio, Na/K, indicates the ratio between the urine sodium concentration and urine potassium concentration, and also the ratio between the renal sodium excretion and renal potassium excretion.

Determination of Chlorides

The chlorides were determined by titration with mercuric nitrate solution (Brun 1949, Krusius 1950). The mercury ions

form with chlorine ions a soluble but practically undissociated mercuric chloride. The indicator used was s-diphenyl carbazone which together with the mercury ions forms a compound reddish violet in colour.

RESULTS OF THE EXPERIMENTS

EXPERIMENTS MADE

1) The water and electrolyte excretion of innervated rabbit kidneys was studied with 5 rabbits in a total of 9 experiments (Table 1).

2) Water and electrolyte excretion after denervation of the left kidney was studied with 8 rabbits in 26 experiments (Table 2).

3) The effect of the distension of the uterus on the water and electrolyte excretion of innervated kidneys was studied with 7 rabbits in 11 experiments (Table 3), and

4) The effect of the distension of the uterus on the water and electrolyte excretion of the kidneys after the denervation of the left kidney was studied with 4 rabbits in 13 experiments (Table 4).

WATER EXCRETION OF THE KIDNEYS

WATER EXCRETION OF INNERVATED KIDNEYS

When studying the water excretion of innervated kidneys experiments were made on rabbits whose ureteral orifices had been transplanted to the abdominal surface but who had both kidneys innervated. The urine excreted by each of the kidneys in successive periods was collected separately and the volume measured. The samples were examined in order to see how the electrolyte excretion of each kidney compared mutually.

Fig. 12. Rabbit II. Nov. 22, 1954. Diuresis produced by 0.45 per cent NaCl. At the beginning of the experiment the left kidney excreted more, then both excreted equal quantities, both had antidiuresis, and at the end of the experiment the right kidney excreted more.

With Rabbit II, Nov. 22, 1954, the left kidney excreted more during the first phase of diuresis and the right kidney more during the second and third phases.

Fig. 13. Rabbit IV. Jan. 6, 1955. Diuresis produced by 0.45 per cent NaCl. At the beginning of the experiment the left kidney excreted more. Then the left kidney had a strong antidiuresis while the right excreted a little. Furthermore, the antidiuresis on the right continued but the left had considerable diuresis. Next, diuresis was equally great on both sides. At the end of the experiment, the diuresis on the right side was greater than on the left side.

Fig. 14. Rabbit III. Dec. 19, 1954. Diuresis produced by 0.45 per cent NaCl. At the beginning of the test the right kidney excreted more. At the end of the test the excretion of both kidneys was roughly equal.

For Rabbit IV, Jan. 6, 1955 it was 4 hours and for Rabbit III, Dec. 19, 1954 4 ½ hours after the beginning of the infusion before a period when both kidneys excreted almost equal quantities.

The water excretion of innervated rabbit kidneys (Table 1) was:

greater on one side almost throughout the test period	in 3 tests
greater alternatingly on one or the other side	» 6 »
Total	9 tests

Conclusion. — The water excretion of innervated rabbit kidneys often differs in volume.

In the course of successive diuretic periods, the left and the right kidney alternate in producing the greater flow of urine.

Discussion. — A comparison of the water excretion of rabbit kidneys with that of dog kidneys reveals a similar variation.

The water excretion of dog kidneys often differs in volume, especially when the urine flow is small (Klisiecki *et al.* 1933a).

With the rabbit, antidiuresis may continue on one side for several hours while the other side has moderate diuresis.

WATER EXCRETION OF THE KIDNEYS AFTER UNILATERAL DENERVATION

The effect of denervation on the water excretion of the homolateral kidney was studied with rabbits whose left kidney was denervated, right kidney innervated, and both ureteral orifices transplanted.

Fig. 15. Rabbit VII. Sept. 28, 1954. Diuresis produced by water. Throughout the test the water excretion of the left and right kidney differed. The individual kidneys alternated in producing a greater flow of water.

Fig. 16. Rabbit XI. May 3, 1955. Diuresis produced by 0.45 per cent NaCl. Almost throughout the test the water excretion of the left and right kidneys differed in volume. The left and the right kidney alternated in excreting more.

Fig. 17. Rabbit X. April 30, 1955. Diuresis produced by 0.45 per cent NaCl. At the beginning of the test there was antidiuresis and the water excretion was equal on both sides. Then the right kidney excreted more. At the end of the test there was antidiuresis and the water excretion was almost equal on both sides.

Rabbit VII, Sept. 28, 1954, Rabbit XI, May 3, 1955 and Rabbit X, April 30, 1955 showed a distinct variation in the water excretion of the left and the right kidney.

The water excretion of the kidneys after the denervation of the left kidney (Table 2) was:

greater on the left side	in	4	tests
greater on the right side	»	3	»
equal on both sides	»	6	»
greater alternatingly on the left and right sides	»	13	»
	Total	26	tests

The length of the period between denervation and the test did not affect the water excretion of the denervated kidney.

Conclusion. — Denervation of the kidney does not appreciably affect its water excretion in unanaesthetized rabbit. The denervated and the innervated kidney alternatingly excrete more urine, or they both excrete equally.

Discussion. — A comparison of the water excretion of a denervated kidney with that of an innervated kidney of unanaesthetized rabbit shows that the results are on the same lines as those reported in the literature from unanesthetized dogs (e.g. Klisiecki *et al.* 1933a, Boylan *et al.* 1953).

EFFECT OF UTERINE DISTENSION ON THE WATER EXCRETION OF INNERVATED KIDNEYS

The effect of distension of the uterus on the water excretion of innervated kidneys was studied from rabbits with an exteriorized uterus, both kidneys innervated, and both ureteral orifices transplanted.

Fig. 18. Rabbit V. March 20, 1955. Diuresis produced by 0.45 per cent NaCl. The uterus was distended by 10 cc. in 45 sec. for 25 min. (2115—2140 hours). Bilateral antidiuresis developed and persisted for half an hour after the distension.

With Rabbit V, March 20, 1955, bilateral antidiuresis was produced by distending the uterus. The water excretion fell fairly fast but not abruptly. The antidiuresis persisted for some time after cessation of the distension. Subsequently the water excretion rose gradually.

Fig. 19. Rabbit VI. Nov. 8, 1954. Diuresis produced by 0.45 per cent NaCl. The uterus was distended in 5 min. by 2 cc. for 1 hour (1130—1230 hours). Slight antidiuresis developed, after which the water excretion rose to its former level. On cessation of the distension a second small antidiuresis followed, after which the water excretion again rose to its former level. The urine from both kidneys was combined in the test.

With Rabbit VI, Nov. 8, 1954, slight antidiuresis was produced on distension of the uterus. The water excretion of the kidneys returned to its former level although the uterus remained distended for one hour. Uterine constrictions were clearly visible in the early stage of the distension. On cessation of the distension a second slight antidiuresis developed, after which the water excretion again returned to its former level.

Fig. 20. Rabbit V. March 25, 1955. Diuresis produced by 0.45 per cent NaCl. At 1310 hours the rabbit was given 1.0 mU (1.0 mU = 1/1000 unit) of pituitrin (Parke, Davis & Co.) intravenously. Antidiuresis developed. The urine from both kidneys was combined in the test.

A comparison of the antidiuresis produced by uterine distension in Rabbit V, March 20, 1955 with that produced by intravenous injection of pituitrin in the same rabbit March 25, 1955 showed no appreciable difference in time relations. Just as the antidiuresis produced by uterine distension, that produced by pituitrin injection also came on fairly fast but not abruptly. The diuresis increased gradually.

The antidiureses obtained with Rabbit VI, Nov. 8, 1954 were similar to those in Rabbit V, March 20, 1955, although smaller and highly transient.

Table 3 shows the percentual drop in the water excretion of innervated kidneys during distension antidiuresis, and the pituitrin dose to which the distension corresponded. The reduced diuresis

due to the distension of the uterus rose to the pre-distension value or higher on both sides in 5 out of 11 tests even before cessation of the distension. In 4 of these tests the distension was done slowly and it was fairly small in volume. In 3 tests antidiuresis persisted on both sides after the distension.

Conclusion. — Distension of the uterus is followed by antidiuresis during which the water excretion of the kidneys falls fairly fast but not abruptly. The rise in diuresis is gradual.

The antidiuresis produced by distending the uterus is similar in time relations to that produced by an intravenous injection of pituitrin.

Discussion. — It has been shown that distension of the rabbit uterus liberates oxytocin (Ferguson 1941) and that emotional stress both inhibits water diuresis and increases uterine activity (Abrahams and Pickford 1954).

In the present investigations it was found that, on distension of the uterus, uterine contractions were sometimes visible during distension antidiuresis. On the other hand, distension antidiuresis was often similar in its course to the antidiuresis produced by intravenous pituitrin injection. Hence it seems probable that distension of the uterus is responsible for the liberation of the antidiuretic and possibly also of the oxytocic fraction of the pituitary.

EFFECT OF UTERINE DISTENSION ON THE WATER EXCRETION OF THE KIDNEYS AFTER UNILATERAL DENERVATION

The effect of distension of the uterus on the water excretion of denervated kidney was studied on rabbits with an exteriorized uterus, innervated right kidney, denervated left kidney, and both ureteral orifices transplanted.

Fig. 21. Rabbit X, May 12, 1955. Diuresis produced by 0.45 per cent NaCl. The uterus was distended in 45 sec. by 10 cc. for 50 min. (2400—0050 hours). At the beginning of the distension antidiuresis developed on both sides.

By distending the uterus in Rabbit X, May 12, 1955, a similar antidiuresis was produced on both sides. The antidiuresis produced by the distension corresponded to that produced by a pituitrin dose of 3 mU.

Fig. 22. Rabbit X, May 26, 1955. Diuresis produced by 0.45 per cent NaCl. At 0345 hours the rabbit was given 1.0 mU pituitrin intravenously, at 0412 2.0 mU, at 0554 3.0 mU and at 0037 4.0 mU. Each pituitrin injection produced a bilateral antidiuresis the extent of which grew with the dose of pituitrin injected.

Pituitrin injections produced a similar antidiuresis on both sides with Rabbit X, May 26, 1955.

The antidiuresis produced in Rabbit X by the distension of uterus and injections of pituitrin showed a similar course.

Fig. 16. Rabbit XI, May 3, 1955. The uterus was distended in 45 sec. by 4 cc. for 15 min. (0035—0050 hours). At the beginning of the distension antidiuresis developed on both sides. At 0125 hours the rabbit was given 0.5 mU of pituitrin intravenously. This was followed by antidiuresis on both sides.

In Rabbit XI, May 3, 1955 bilateral antidiuresis was produced by distending the uterus. The antidiuresis corresponded to that resulting from a pituitrin dose > 0.5 mU.

The antidiuresis produced by uterine distension and the pituitrin injection were similar in course in Rabbit XI also.

Fig. 17. Rabbit X, April 30, 1955. The uterus was distended in 45 sec. by 3 cc. for 20 min. (2145—2205 hours). At the beginning of the distension, antidiuresis developed on both sides and was not yet past when the experiment was terminated.

In Rabbit X, April 30, 1955 a similar antidiuresis on both sides was produced by distending the uterus.

Table 4 shows the percentual drop in the water excretion of each of the kidneys produced by the distension and the pituitrin dose to which the distension corresponded. In 2 out of 13 experiments the reduction in water excretion due to uterine distension ceased or the excretion rose above the initial value on both sides before the distension was discontinued.

The water excretion of the kidneys during the distension antidiuresis was:

higher on the left side	in	3	tests
higher on the right side	»	4	»
equal on both sides	»	5	»
alternatingly higher on one side or the other..	»	1	»
Total		13	tests

The water excretion of the kidneys during the antidiuresis produced by pituitrin injections was:

higher on the left side	in	5	tests
higher on the right side	»	3	»
equal on both sides	»	6	»
alternatingly higher on one side or the other ..	»	3	»
	Total	17	tests

Conclusion. — An antidiuresis similar in course develops on both the denervated and the innervated side on distension of the uterus.

Intravenous injection of pituitrin produces a similar antidiuresis on both the denervated and the innervated side.

Distension of the uterus and exogenous administration of pituitrin may produce a similar antidiuresis.

Discussion. — Antidiuresis produced by distension of the uterus sets in as fast and as strong on the denervated as on the innervated side. On the other hand, the antidiuresis often lasts longer than the distension. Or, if the distension is of short duration, the maximum antidiuresis is only reached after the distension. These points support the assumption that a mechanism slower than nervous irritation, probably just hormonal action, is responsible for producing antidiuresis.

SODIUM EXCRETION OF THE KIDNEYS

SODIUM EXCRETION OF INNERVATED KIDNEYS

The sodium and chloride concentrations of urine excreted by innervated kidneys were determined from the urine passed in consecutive periods. The sodium excretion and sodium: potassium ratio were computed.

Fig. 13. Rabbit IV, Jan. 6, 1955. The sodium concentration and the chloride concentration were higher on the right side almost the whole time. It was only at the end of the test that they first became equal and, then, higher on the left side.

In Rabbit IV, Jan. 6, 1955 the urine sodium concentration was higher on the right side which excreted less urine. As the water excretion of the right kidney increased its sodium concentration fell

below that of the opposite side. The chloride concentration also was higher on the side excreting less urine. The sodium excretion was higher on the side excreting more urine. When the water excretion of the kidneys was almost equal the sodium excretion of the two sides was also approximately equal. No typical differences were noted in the sodium: potassium ratio between the sides.

Fig. 14. Rabbit III. Dec. 19, 1954. Sodium concentration and chloride concentration were higher on the left side.

In Rabbit III, Dec. 19, 1954 the results were similar to those for Rabbit IV, Jan. 6, 1955.

Conclusion. — When the water excretion of innervated rabbit kidney is low the sodium concentration in the urine excreted by it is high, and vice versa. When the water excretion of innervated kidneys is approximately equal the sodium concentrations of the different sides are almost equal.

The chloride concentration is higher when the water excretion is low than when the water excretion is copious.

The sodium excretion is usually higher in the kidney excreting more urine. When the water excretion of innervated kidneys is approximately equal their sodium excretion also is almost equal.

Discussion. — The excretion of sodium and of urine by dog during water diuresis has been studied by Karvonen and Leppänen (1952). The sodium excretion was usually parallel with the volume of urine excreted, although there were exceptions.

The results of the present investigations, with rabbits, were parallel to those obtained by Karvonen and Leppänen (1952) with dogs.

SODIUM EXCRETION AFTER UNILATERAL DENERVATION

The effect of denervation of the left kidney on its sodium excretion was studied by comparing it with that of the right, innervated kidney.

Fig. 15. Rabbit VII. Sept. 28, 1954. The sodium concentration was higher on one side or the other in turn.

Fig. 16. Rabbit XI, May 3, 1955. The sodium concentration and chloride concentration were higher on one side or the other in turn.

With Rabbit VII, Sept. 28, 1954 and Rabbit XI, May 3, 1955 the urine sodium concentration was higher alternatingly on either

side and so was the chloride concentration with Rabbit XI May 3, 1955. The sodium excretion fluctuated in both tests, higher now on one side, now on the other. It was often higher on the side excreting more urine. No typical differences were noted in the sodium: potassium ratio between the sides.

The sodium concentration of the urine (Table 2) was:

higher on the left side	in	3	tests
higher on the right side	»	2	»
equal on both sides	»	5	»
alternatingly higher on one side or the other . .	»	16	»
Total		26	tests

The urine chloride concentration was studied by 17 tests. It was:

higher on the left side	in	3	tests
higher on the right side	»	1	»
equal on both sides	»	5	»
alternatingly higher on one side or the other . .	»	8	»
Total		17	tests

The sodium excretion of the kidneys was:

higher on the left side	in	3	tests
higher on the right side	»	3	»
equal on both sides	»	6	»
alternatingly higher on one side or the other . .	»	14	»
Total		26	tests

Conclusion. — Denervation of the kidney does not essentially affect the sodium and chloride concentration of the urine or the renal sodium excretion of a conscious rabbit.

Discussion. — A comparison of the sodium excretion of the denervated and the innervated kidney of conscious rabbit shows results similar to those reported in the literature from conscious dogs (e.g. Berne 1952).

EFFECT OF UTERINE DISTENSION ON THE SODIUM EXCRETION OF INNERVATED KIDNEYS

As pointed out above, every effort was made to distend the uterus at as stable a stage of urine excretion as possible. This pre-

caution made it possible to study the urine collected in consecutive periods, and so to find out the effect of uterine distension on sodium excretion.

Fig. 18. Rabbit V, March 20, 1955. On distension of the uterus, the urine sodium concentration rose on both sides.

Fig. 20. Rabbit V, March 25, 1955. After pituitrin injection the sodium and chloride concentration rose.

In Rabbit V, March 20, 1955 the sodium concentration increased considerably during the antidiuresis produced by distending the uterus. By the time the antidiuresis had ceased the sodium concentration fell to its former level. Sodium excretion was reduced during the distension antidiuresis.

On intravenous injection of pituitrin into Rabbit V, March 25, 1955 the sodium concentration increased during the resulting antidiuresis. By the time the antidiuresis had passed the sodium concentration was back at its former level. Sodium excretion was reduced during the pituitrin-induced antidiuresis. No typical differences were noted in the sodium: potassium ratio between the two methods, distension of the uterus and injection of pituitrin.

Table 3 shows the percentual decrease in renal sodium excretion during antidiuresis produced by distension. In 8 out of 11 tests, the sodium excretion returned to its former level on both sides before the distension was discontinued. In one test the sodium excretion increased throughout the distension.

Conclusion. — On distension of the uterus, during antidiuresis, a rise in the urine sodium concentration of innervated kidneys is noted. While the antidiuresis is passing the sodium concentration drops. Sodium excretion is reduced at the beginning of distension antidiuresis.

During the antidiuresis produced by intravenous pituitrin injection, too, the urine sodium concentration increases. With the antidiuresis over, the sodium concentration declines. Sodium excretion decreases during pituitrin-induced antidiuresis.

Discussion. — As a parallel change in the urine sodium excretion is produced both by distending the uterus and by intravenous injection of pituitrin, it seems increasingly probable that the posterior pituitary hormone at least contributes to the development of distension antidiuresis.

EFFECT OF UTERINE DISTENSION ON RENAL SODIUM EXCRETION AFTER UNILATERAL DENERVATION

The effect of distension of the uterus on sodium excretion was studied after the denervation of the left kidney, the right kidney being left intact.

Fig. 21. Rabbit X. May 12, 1955. On distension of the uterus, the urine sodium and chloride concentrations increased on both sides.

Fig. 22. Rabbit X, May 26, 1955. Rising doses of pituitrin were given intravenously. After each injection the urine sodium and chloride concentration increased on both sides.

When the uterus of Rabbit X, May 12, 1955 was distended the urine sodium and chloride concentrations rose on both sides at the same time as antidiuresis set in. As the diuresis rose to its former level the sodium and chloride concentrations declined a little. Sodium excretion decreased during the distension antidiuresis.

On intravenous injections of rising doses of pituitrin into Rabbit X, May 26, 1955 the urine sodium and chloride concentrations rose on both sides during the resulting antidiuresis. Sodium excretion decreased after the injections. No regular variation occurred in the sodium: potassium ratio.

Fig. 16. Rabbit XI. May 3, 1955. On distension of the uterus the urine chloride concentration rose on both sides. The rise in the sodium concentration was not quite so distinct on the left side. An intravenous injection of pituitrin was followed by a slight rise in the sodium concentration on both sides, but no change was noted in the chloride concentration.

The urine sodium concentration during distension antidiuresis was:

higher on the left side	in	3	tests
higher on the right side	»	3	»
equal on both sides	»	6	»
alternatingly higher on one side or the other ..	»	1	»
Total		13	tests

The urine chloride concentration during the distension antidiuresis was:

higher on the left side	in	3	tests
higher on the right side	»	3	»
equal on both sides	»	7	»
alternatingly higher on one side or the other	»	—	»
Total		13	tests

The renal sodium excretion during the distension antidiuresis was:

higher on the left side	in	5	tests
higher on the right side	»	5	»
equal on both sides	»	2	»
alternatingly higher on one side or the other	»	1	»
Total		13	tests

Table 4 shows the percentual drop in the sodium excretion of both kidneys during the antidiuresis produced by distension. On both sides, sodium excretion rose to its former level in 4 out of 13 tests before the distension was discontinued, and exceeded considerably the pre-distension value in 1 test.

The urine sodium concentration during the pituitrin-induced antidiuresis was:

higher on the left side	in	7	tests
higher on the right side	»	5	»
equal on both sides	»	—	»
alternatingly higher on one side or the other	»	5	»
Total		17	tests

The urine chloride concentration during pituitrin-induced antidiuresis was:

higher on the left side	in	10	tests
higher on the right side	»	5	»
equal on both sides	»	1	»
alternatingly higher on one side or the other	»	1	»
Total		17	tests

The renal sodium excretion during pituitrin-induced antidiuresis was:

higher on the left side	in	6	tests
higher on the right side	»	5	»
equal on both sides	»	2	»
alternatingly higher on one side or the other	»	4	»
Total		17	tests

Conclusion. — On distension of the uterus, during antidiuresis, the sodium and chloride concentrations in the urine of both the denervated and the innervated kidney increase. When the anti-

diuresis ceases the sodium and chloride concentrations decline on both sides. Sodium excretion is reduced on both sides during distension antidiuresis.

During pituitrin-induced antidiuresis, the sodium and chloride concentrations in the urine of both the denervated and the innervated kidney increase. When the antidiuresis ceases the sodium and chloride concentrations fall on both sides. Sodium excretion decreases on both sides during antidiuresis produced by pituitrin injection.

Discussion. — The change in the sodium concentration and sodium excretion on distension of the uterus and on injection of pituitrin is similar on the denervated and innervated side. In addition, distension of the uterus and injection of pituitrin produce changes on the same lines in the sodium concentration, and in the sodium excretion.

POTASSIUM EXCRETION OF THE KIDNEYS

POTASSIUM EXCRETION OF INNERVATED KIDNEYS

The potassium concentrations of urine excreted by each of two innervated kidneys in consecutive periods were determined and the potassium excretion of the kidneys was computed.

Fig. 13. Rabbit IV. Jan. 6, 1955. The potassium concentration at the beginning of the test was higher on the right side and at the end of the test on the left side.

In Rabbit IV, Jan. 6, 1955, the urine potassium concentration was higher at the beginning of the test on the right side which excreted less urine. When the water excretions of the two kidneys approached the same level the potassium concentrations became almost equal. At the end of the test the potassium concentration was higher on the left side which excreted less urine. Potassium excretion was higher on the side that excreted more urine.

Fig. 14. Rabbit III, Dec. 19, 1954. The potassium concentration at the beginning was higher on the left side; at the end of the test it was equal on both sides.

The results with Rabbit III Dec. 19, 1954, were similar to those for Rabbit IV, Jan. 6, 1955.

Conclusion. — When the water excretion by innervated rabbit kidney is low the potassium concentration of the urine excreted by it is high. When the water excretions by innervated kidneys are equal the potassium concentrations are equal.

More potassium is usually excreted by the side excreting more urine. When the water excretion of the kidneys is equal their potassium excretion also is equal.

Discussion. — A comparison between the potassium excretion and sodium excretion of innervated rabbit kidneys shows a similar regularity. The results are similar to those obtained by Friberg *et al.* with dog (1950).

POTASSIUM EXCRETION AFTER UNILATERAL DENERVATION

The effect of the denervation of the left kidney on its potassium excretion was studied by comparing it with the potassium excretion of the right, innervated kidney.

Fig. 15. Rabbit VII, Sept. 28, 1954. The potassium concentration was higher on the left and right sides in turn.

Fig. 16. Rabbit XI, May 3, 1955. The potassium concentration was higher on one side or the other in turn.

With Rabbit VII, Sept. 28, 1954, and Rabbit XI, May 3, 1955, the potassium concentration and potassium excretion was alternatingly higher on one side or the other.

Urine potassium concentration (Table 2) was:

higher on the left side	in	3	tests
higher on the right side	»	2	»
equal on both sides	»	7	»
alternatingly higher on one side or the other	»	14	»
Total		26	tests

The renal potassium excretion was:

higher on the left side	in	3	tests
higher on the right side	»	3	»
equal on both sides	»	6	»
alternatingly higher on one side or the other	»	14	»
Total		26	tests

Conclusion. — Denervation of the kidney does not essentially affect the urine potassium concentration or renal potassium excretion of unanaesthetized rabbit.

Discussion. — A comparison of the potassium excretion by the denervated and innervated kidney of unanaesthetized rabbit with the results obtained by Surtshin *et al.* (1952) with dog reveals similar findings.

EFFECT OF UTERINE DISTENSION ON THE POTASSIUM EXCRETION OF INNERVATED KIDNEYS

Fig. 18. Rabbit V. March 20, 1955. On distension of the uterus the urine potassium concentration rose on both sides.

Fig. 20. Rabbit V, March 25, 1955. After pituitrin injection the potassium concentration rose.

With Rabbit V, March 20, 1955, when the uterus was distended, it was noted that during the resulting antidiuresis the urine potassium concentration increased on both sides. When the diuresis began to increase the potassium concentration dropped. Potassium excretion was reduced during the distension antidiuresis.

When Rabbit V, March 25, 1955, was given an intravenous injection of pituitrin the potassium concentration rose during the resulting antidiuresis; it was at its highest just after the antidiuretic maximum had passed. When the diuresis increased to its former level the potassium concentration declined to its pre-injection level. Excretion of potassium decreased in the initial phase of the pituitrin-induced antidiuresis. Subsequently there was a secondary rise. By the time the diuresis had returned to its former level the potassium excretion also assumed the pre-injection level.

Table 3 shows the percentual decrease in potassium excretion by both kidneys during the antidiuresis produced by distension. In 6 out of 11 tests the potassium excretion rose to its former level before the distension ceased. In 2 tests the potassium excretion rose throughout the distension on both sides, and in 1 test on the right side.

Conclusion. — On distension of the uterus, during antidiuresis, the urine potassium concentration of innervated kidneys increases. When the antidiuresis passes the potassium concentration declines. Potassium excretion is reduced during distension antidiuresis.

During pituitrin-induced antidiuresis, too, the urine potassium concentration rises. When the antidiuresis passes the potassium concentration declines. Potassium excretion declines during pituitrin-induced antidiuresis.

Discussion. — Distending the uterus and intravenous injection of pituitrin produce changes on the same lines in the urine potassium concentration, and in the renal potassium excretion. The results are similar to those obtained in investigations into urine sodium excretion.

In some tests the excretion of potassium showed a secondary rise before the passing of the antidiuresis due to the pituitrin injection. But by the time the diuresis had returned to its original level the potassium excretion declined to the pre-injection level.

EFFECT OF UTERINE DISTENSION ON RENAL POTASSIUM EXCRETION AFTER UNILATERAL DENERVATION

The effect of uterine distension on the excretion of potassium was studied after the denervation of the left kidney, the right kidney left intact.

Fig. 21. Rabbit X. May 12, 1955. On distension of the uterus the urine potassium concentration rose on both sides.

Fig. 22. Rabbit X. May 26, 1955. Rising doses of pituitrin were given intravenously. After each injection the urine potassium concentration increased on both sides.

When the uterus of Rabbit X, May 12, 1955, was distended the urine potassium concentration increased on both sides. When the antidiuresis passed the urine potassium concentration decreased. Potassium excretion declined during the antidiuresis produced by distension.

Rising doses of pituitrin injected intravenously into Rabbit X, May 26, 1955, raised the urine potassium concentration during the resulting antidiuresis on both sides. Excretion of potassium was reduced after the pituitrin injections.

The urine potassium concentration during the antidiuresis produced by distension was:

higher on the left side	in	2	tests
higher on the right side	»	—	»
equal on both sides	»	6	»
alternatingly higher on one side or the other ..	»	5	»
Total		13	tests

The excretion of potassium by the kidneys during the antidiuresis produced by distension was:

higher on the left side	in	4	tests
higher on the right side	»	5	»
equal on both sides	»	1	»
alternatingly higher on one side or the other ..	»	3	»
Total		13	tests

Table 4 shows the percentual decrease in the excretion of potassium by both kidneys during the distension antidiuresis. Potassium excretion increased to its former level on both sides in 4 out of 13 tests before the distension was discontinued.

The urine potassium concentration during the pituitrin-induced antidiuresis was:

higher on the left side	in	4	tests
higher on the right side	»	3	»
equal on both sides	»	4	»
alternatingly higher on one side or the other ..	»	6	»
Total		17	tests

The excretion of potassium by the kidneys during the pituitrin-induced antidiuresis was:

higher on the left side	in	5	tests
higher on the right side	»	4	»
equal on both sides	»	2	»
alternatingly higher on one side or the other ..	»	6	»
Total		17	tests

Conclusion. — On distension of the uterus, during antidiuresis, the urine potassium concentration of both the denervated and the innervated kidney increases. When the antidiuresis passes the potassium concentration drops on both sides. Excretion of potassium decreases on both sides during distension antidiuresis.

During antidiuresis produced by an intravenous injection of pituitrin the urine potassium concentration of both the denervated and the innervated kidney increases. When the antidiuresis passes the potassium concentration decreases on both sides. Potassium excretion decreases on both sides during pituitrin-induced antidiuresis.

Discussion. — On distension of the uterus and injection of pituitrin the change in the urine potassium concentration and potassium excretion is similar on the denervated and innervated side. In addition, distension of the uterus and exogenous administration of pituitrin produce changes on the same lines in the urine potassium concentration, and in the renal potassium excretion.

DISCUSSION

Excretion by Innervated Kidneys. As was reported in the survey of the literature, Verney (1930) and Klisiecki *et al.* (1933a) observed that the two innervated kidneys of dog excreted different volumes of urine.

Verney explains this by stating that some of the excreting units of the kidney may remain at rest on one side while on the other a greater number of them is in function. Accepting this, the urine volumes of individual kidneys may remain different for lengthy periods even, as was the case in the present experiments with rabbits.

Denervation of the Kidney. Different methods have been applied in the denervation of the kidney. It is difficult to know whether the kidney is totally denervated. It has been claimed that total surgical denervation of the kidney can only be effected by severing the renal artery, renal vein and ureter and by resuturing them (Quinby 1916). In practice this would be a difficult operation to perform, almost impossible. A less injurious method is required. In the present investigations it was considered sufficient to divide the splanchnic nerve.

Irrespective of the denervation technique, a common feature of the present results and those reported in the literature is that in an unanaesthetized experimental animal denervation of the kidney does not affect the electrolyte concentration of the urine excreted, or the excretion of water and electrolytes. Where the denervation did affect these factors the animals were anaesthetized.

In the present experiments on 10 anaesthetized rabbits, not reported above, the average water excretion was greater in the denervated than in the innervated kidney.

Distension of the Uterus. When the uterus is distended e.g. in 45 seconds by 10 cc., stretching of the uterine wall might be considered unphysiological. Indisputably, the tests

give slightly differing results depending on the initial rate, volume and duration of the distension.

When the uterus is distended by 2 cc. in 5 minutes for 1 hour, done e.g. to Rabbit VI, Nov. 8, 1954 (Fig. 19), a slight rapidly transient antidiuresis, nevertheless of the pituitrin type, is produced at the beginning of the distension. Even when the distension is continued, water excretion subsequently increases and then continues unchanged. On cessation of the distension another similar antidiuresis may set in.

If the distension is done quickly and is of a greater volume, a strong antidiuresis sets in and continues even after the end of the distension. The electrolyte concentration increases markedly during the antidiuresis.

Distension Antidiuresis. The antidiuresis developing on distension of the uterus is similar on both the innervated and the denervated side. The antidiuresis may persist longer than the distension. In addition, antidiuresis produced by uterine distension and by intravenous pituitrin injection are similar in their time relations and, often, in their course. Furthermore, distension of the uterus and intravenous injection of pituitrin have an effect on the same lines on the urine sodium, chloride and potassium concentrations, and on the excretion of sodium and potassium.

From the above, it may be assumed that distension of the uterus liberates the pituitary antidiuretic factor; hence secretion of posterior pituitary hormone plays at least some part in the etiology of antidiuresis. Another factor, at the beginning of the distension, is probably emotional stress which also apparently stimulates secretion of the posterior pituitary hormone (Rydin and Verney 1938, Abrahams and Pickford 1954).

The rise in the electrolyte concentration during distension antidiuresis probably results from pituitrin secretion. Apparently tubular reabsorption is reduced, resulting in an increase in the concentrations of sodium, chlorides and potassium (Shannon 1942, Anslow and Wesson 1955).

Significance of Distension Results. The following points from the experiments are worth noting:

1. Water excretion by the kidneys may rise to its former level or even exceed the pre-distension value before the distension is discontinued, even when a high distension volume is applied.

2. Low volume distension started slowly produces a rapidly transient, small antidiuresis. Even if the distension is continued renal water excretion increases immediately to its former level after the small antidiuresis.

3. Excretion of sodium and potassium by the kidneys may considerably exceed the pre-distension values even before the distension is discontinued, and this holds good also for a high distension volume.

4. Distension of the uterus produces a similar change in the diuresis, and electrolyte excretion of both innervated and denervated kidney. The change produced, moreover, is *similar* to that produced by an intravenous injection of pituitrin.

According to the supporters of the Trueta theory, a diversion of the bloodstream occurs in the kidneys on distension of the uterus. If this is so, it naturally also plays a part in the origination of antidiuresis.

In order to throw light on the significance of the utero-renal reflex, Franklin (1955) studied the effect of the vagino-renal reflex on diuresis. It was by distending the vagina, also, that changes were produced in the renal surface suggestive of diversion of the renal bloodstream. Distension of rabbit vagina for 14 days reduced water excretion by the kidneys by 31—52 per cent. But it should be borne in mind that the daily water excretion varies to some extent in normal conditions even (Black and Thomson 1951).

The fact that uterine distension produced no pallor or only a slight degree of pallor of the denervated kidney in Franklin's and in the present experiments with 6 rabbits, not listed above, may be due to the observations having been made under anaesthesia. Anaesthesia is responsible for the vasoconstriction of the innervated kidney, but only to a small degree for vasoconstriction in the denervated kidney (Miles and de Wardener 1952).

In the present series of experiments, distension of the uterus did not seem to have any immediate effect on the renal function. Division of the splanchnic nerve did not affect the change in renal excretion produced by distension of the uterus as this change was noted even when the splanchnic nerve was divided.

It is improbable that a stimulus such as uterine distension will produce a change in the secretion of a particular hormone

only. Possibly also the other hormones are involved, but these changes may be too small to be stated.

In none of the present distension experiments was an increased potassium excretion with a decreased sodium excretion observed as typical of most of the adrenocortical hormones. If 5-hydroxytryptamine is taken as a hormone, even it seemed unable to produce a typical antidiuresis such as was done here by uterine distension.

In the present investigations the only observable uterorenal reflex was a transient liberation of pituitary antidiuretic hormone.

SUMMARY

Survey of the Literature. The survey of the literature discusses the renal function mechanism, the influence of humoral and nervous factors on the renal excretion, and the connection between the uterus and the kidney.

Experimental Animals and Operations. The experimental animals consisted of 14 rabbits, operated on as follows:

a) Denervation of the left kidney by division of the left splanchnic nerve was performed on 8 rabbits. A microscopic preparation was made of the resected piece of nerve.

b) Transplantation of the ureters was performed on all the 14 rabbits.

c) Exteriorization of the uterus was performed on 11 rabbits.

Technique of Experiments. The experiments were carried out on unanaesthetized animals 8—12 days after the operation. To produce a diuresis, the animals were given a continuous infusion of 0.45 per cent NaCl or, in some tests, water by stomach tube. The urine volume excreted by each of the kidneys was measured at 5-minute intervals. It was collected separately from each kidney for determination of sodium, chlorides and potassium.

Distension of the uterus. The uterus was distended by a rubber balloon, which, collapsed, was introduced into the uterine cornu in the phase when the urine excretion was stable. The uterus was distended in 45 sec. — 5 min. for 10 min. — 2 hours by a volume of 2—10 cc. by injecting water at +37°C into the balloon.

Laboratory Studies. The sodium and potassium were determined from the urine samples by flame photometer with lithium as the internal standard.

The chlorides were determined by titration according to Brun.

EXPERIMENTS.

1. Excretion of water, sodium and potassium by innervated rabbit kidneys was studied with 5 rabbits in 9 experiments.

2. The effect of unilateral denervation on the excretion of water, sodium and potassium by the homolateral kidney was studied by comparing it with the corresponding excretion by the opposite, innervated kidney; 26 experiments were made with 8 rabbits.

3. The effect of distension of the uterus on the excretion of water, sodium and potassium by innervated kidneys was studied with 7 rabbits in 11 experiments.

4. Finally, the effect of distension of the uterus on the excretion of water, sodium and potassium by the denervated kidney was studied by comparing it with the corresponding excretion of the opposite, innervated kidney; 13 experiments were made with 4 rabbits.

The following results were obtained:

WATER EXCRETION BY THE KIDNEYS

1. Water excretion of the individual innervated kidneys of rabbit is often different.

2. Denervation of the kidney does not essentially affect the water excretion by the homolateral kidney of unanaesthetized rabbit.

3. Distension of the uterus produces an antidiuresis which is similar on both the innervated and the denervated side.

4. An intravenous injection of pituitrin (0.5—4.0 mU) produces an antidiuresis similar in time relations to that produced by uterine distension. The antidiuresis is similar on both the innervated and the denervated side.

SODIUM AND POTASSIUM EXCRETION BY THE KIDNEYS

1. In the urine excreted by innervated kidneys, the concentration of sodium, chlorides and potassium is often higher on the side excreting less urine.

The excretion of sodium and potassium is often higher on the side excreting more urine.

2. Denervation of the kidney does not essentially affect the

urine sodium, chloride and potassium concentrations or the sodium and potassium excretion in unanaesthetized rabbit.

3. During the antidiuresis produced by distension of the uterus the urine sodium, chloride and potassium concentration increases, the sodium and potassium excretion decreases. The change is similar on both the innervated and the denervated side.

4. Intravenous injection of pituitrin (0.5—4.0 mU) produces during antidiuresis an increase in the urine sodium, chloride and potassium concentration and a decrease in the sodium and potassium excretion. The change is similar on both the innervated and the denervated side.

APPENDIX

FIGURES and TABLES

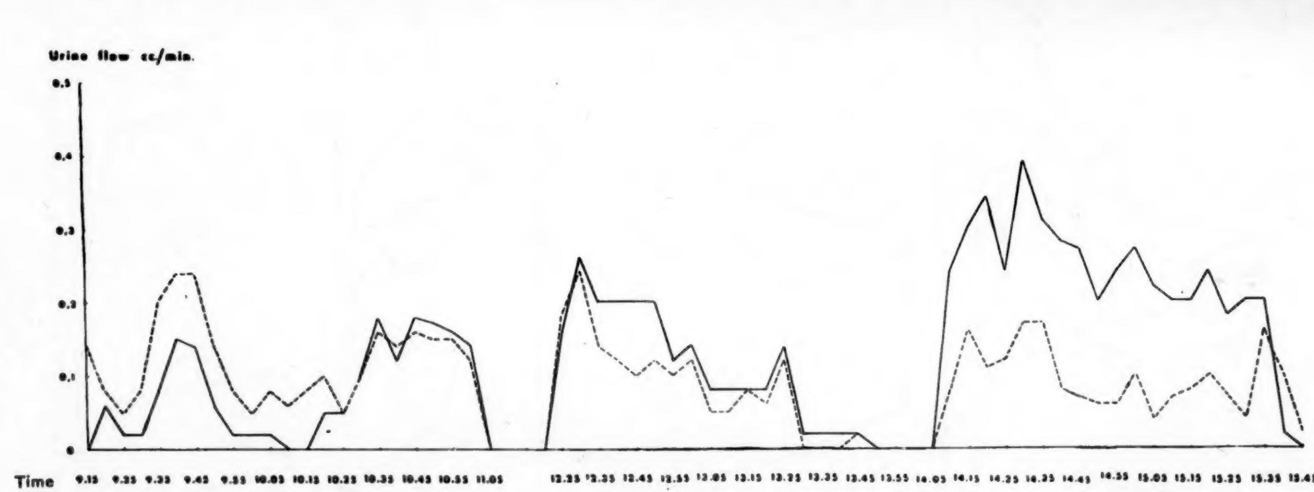

Fig. 12.

Rabbit II 22. 11. 54

----- left, innervated ——— right, innervated

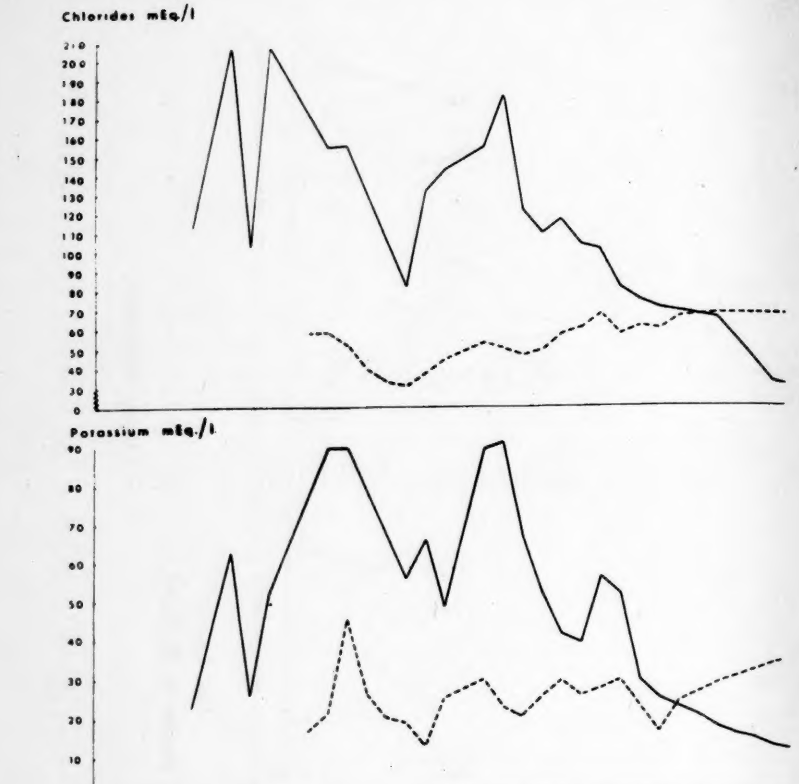

Fig. 13.

Rabbit IV 6. I. 55

----- **left, innervated** ——— **right, innervated**

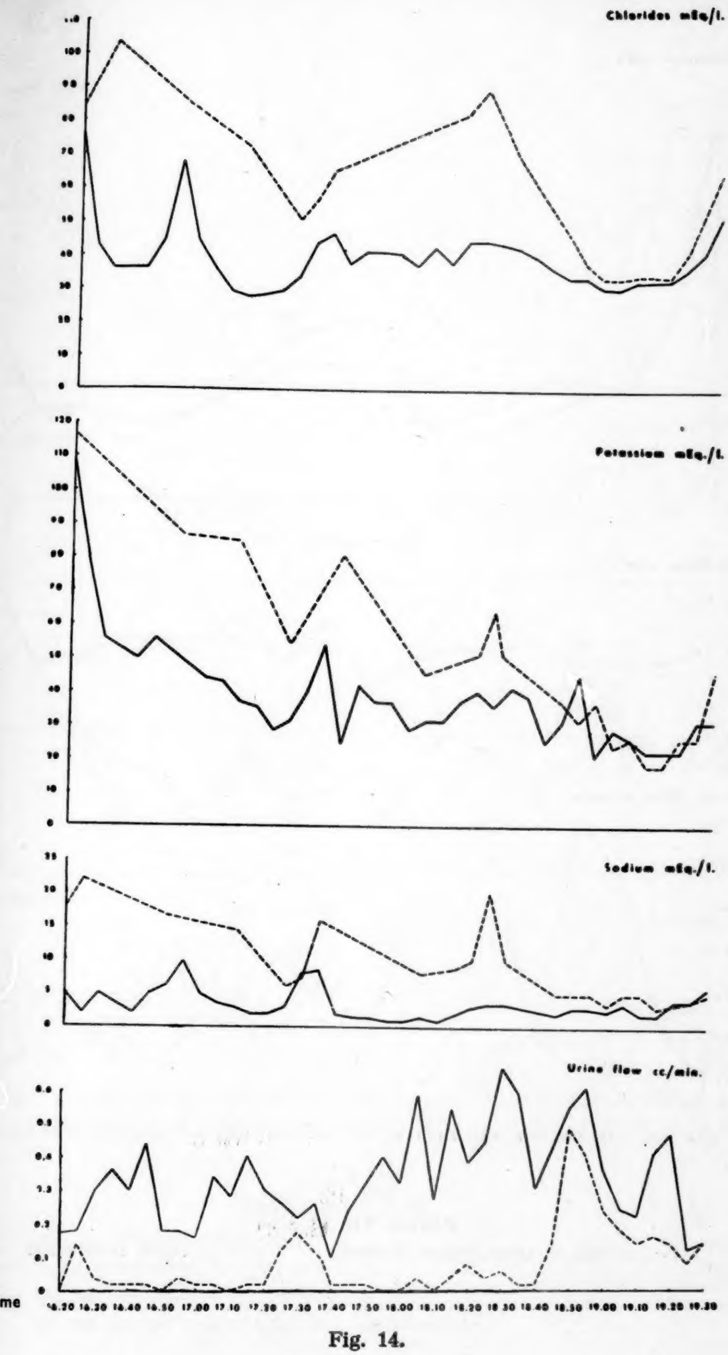

Fig. 14.

Rabbit III 19. 12. 54

----- left, innervated ——— right, innervated

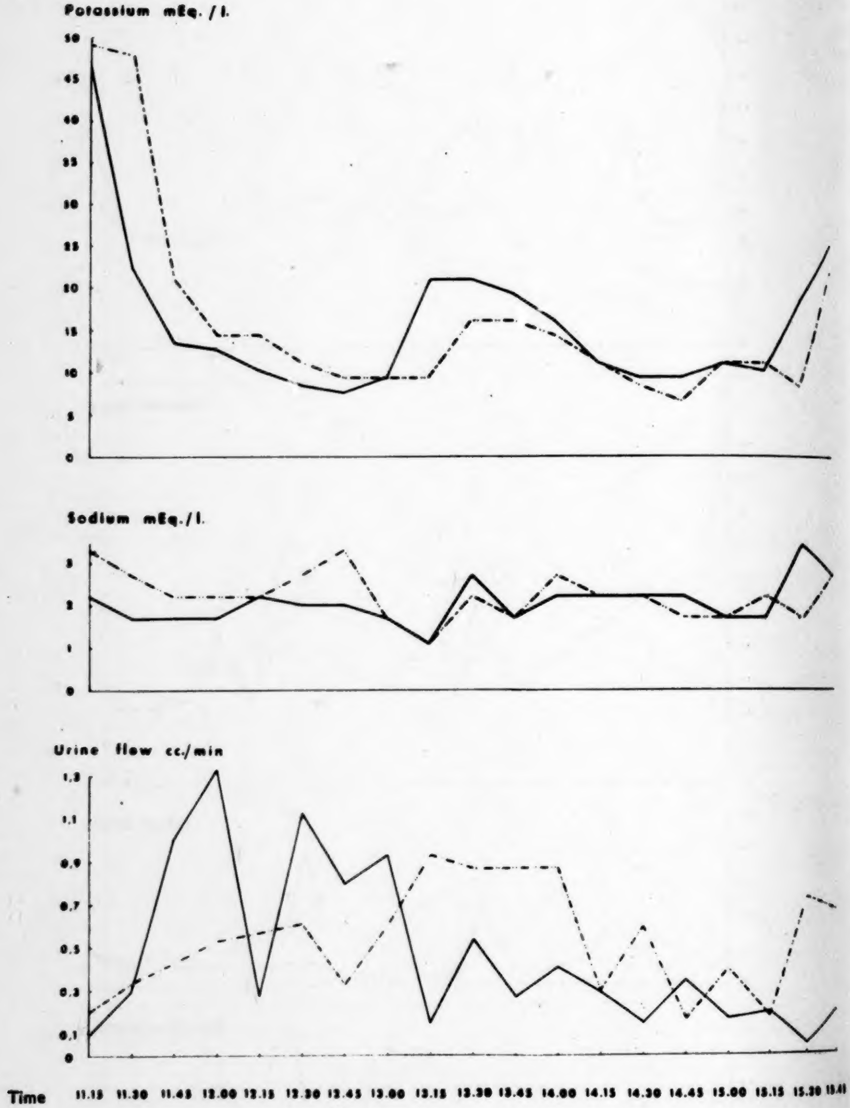

Fig. 15.

Rabbit VII 28. 9. 54

–·–·– left, n. splanchnicus divided. ——— right, innervated

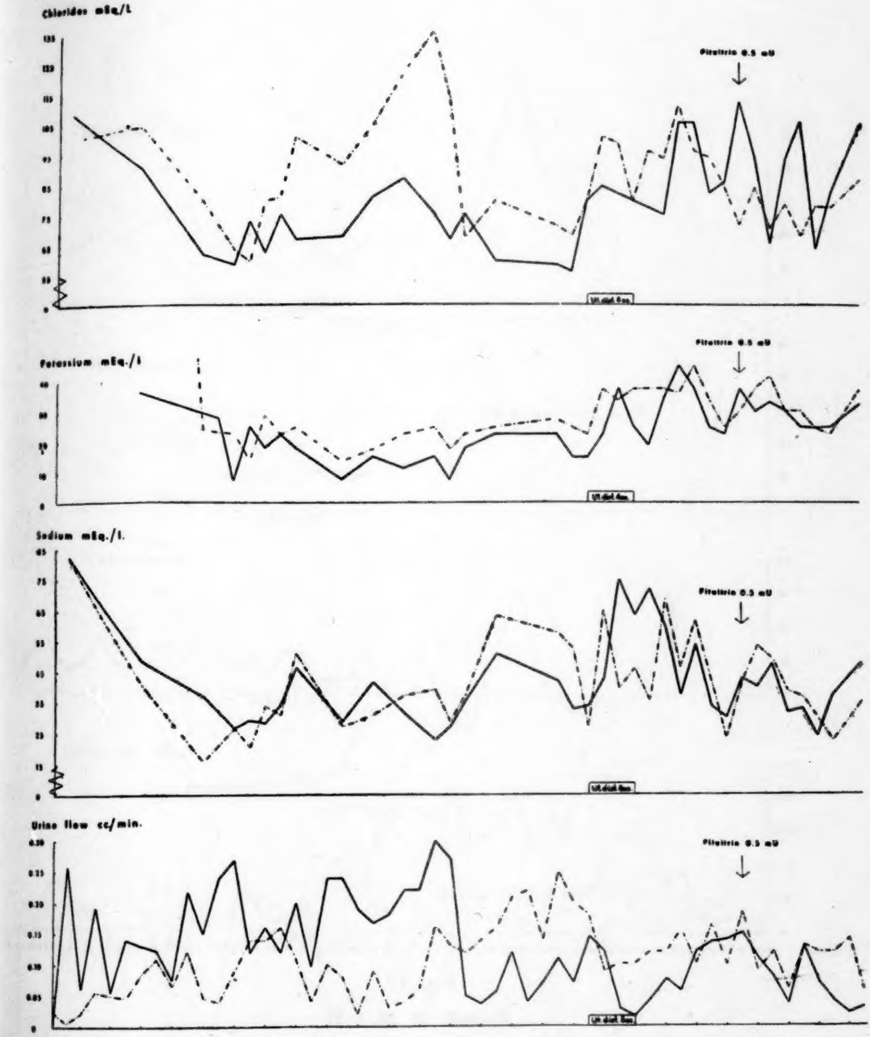

Fig. 16.

Rabbit XI 3. 5. 55

-·-·-·- **left, n. splanchnicus divided**

——— **right, innervated**

▭ **Uterus distended 4 cc. 15 min.**

At the arrows pituitrin 0.5 mU intravenously

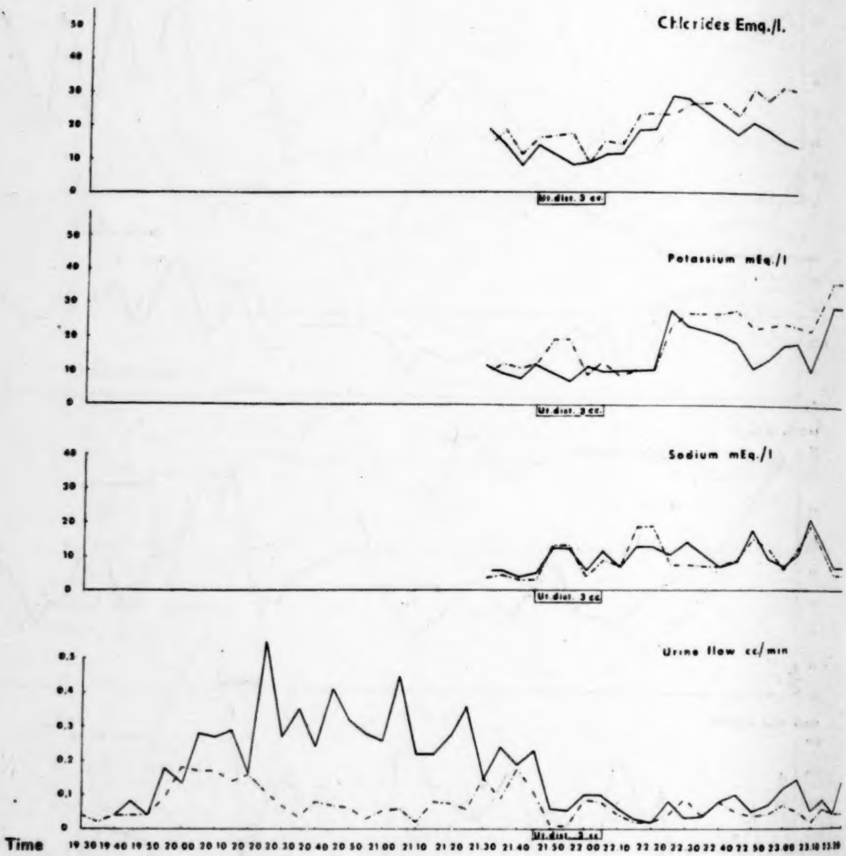

Fig. 17.

Rabbit X 30. 4. 55

–·–·–·– left, n. splanchnicus divided. ——— right, innervated

Uterus distended 3 cc. 20 min.

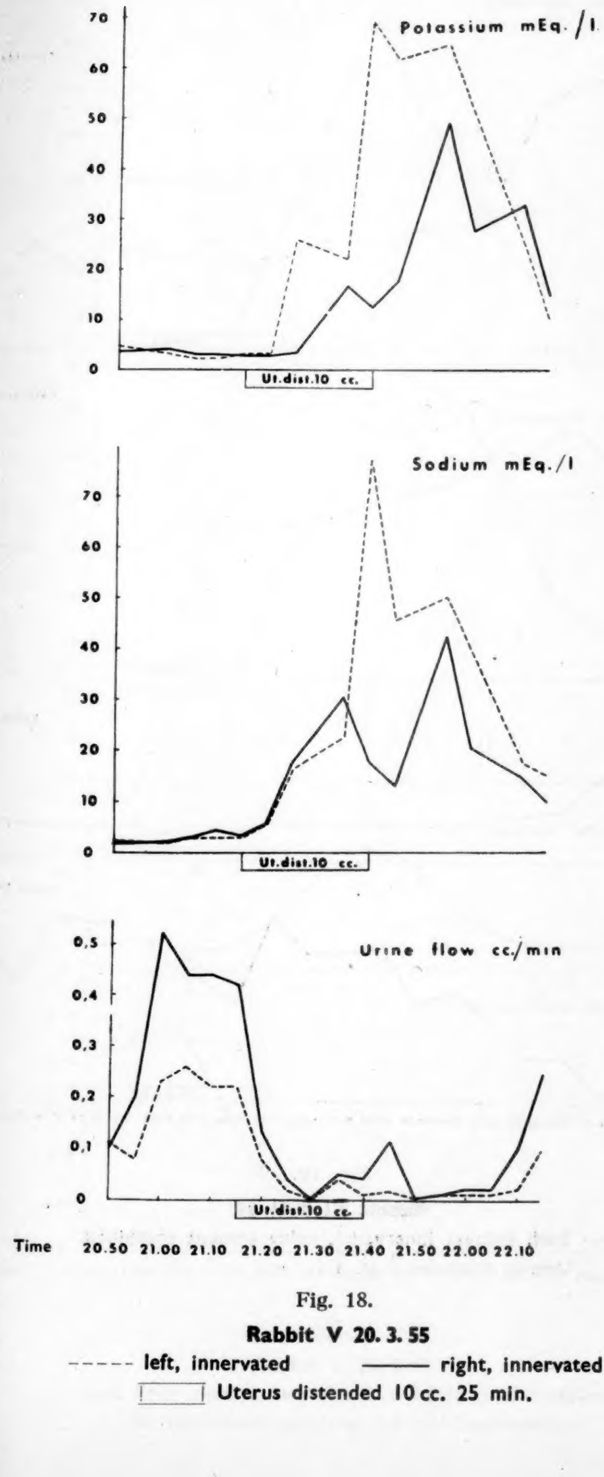

Fig. 18.

Rabbit V 20. 3. 55

----- **left, innervated** ——— **right, innervated**

Uterus distended 10 cc. 25 min.

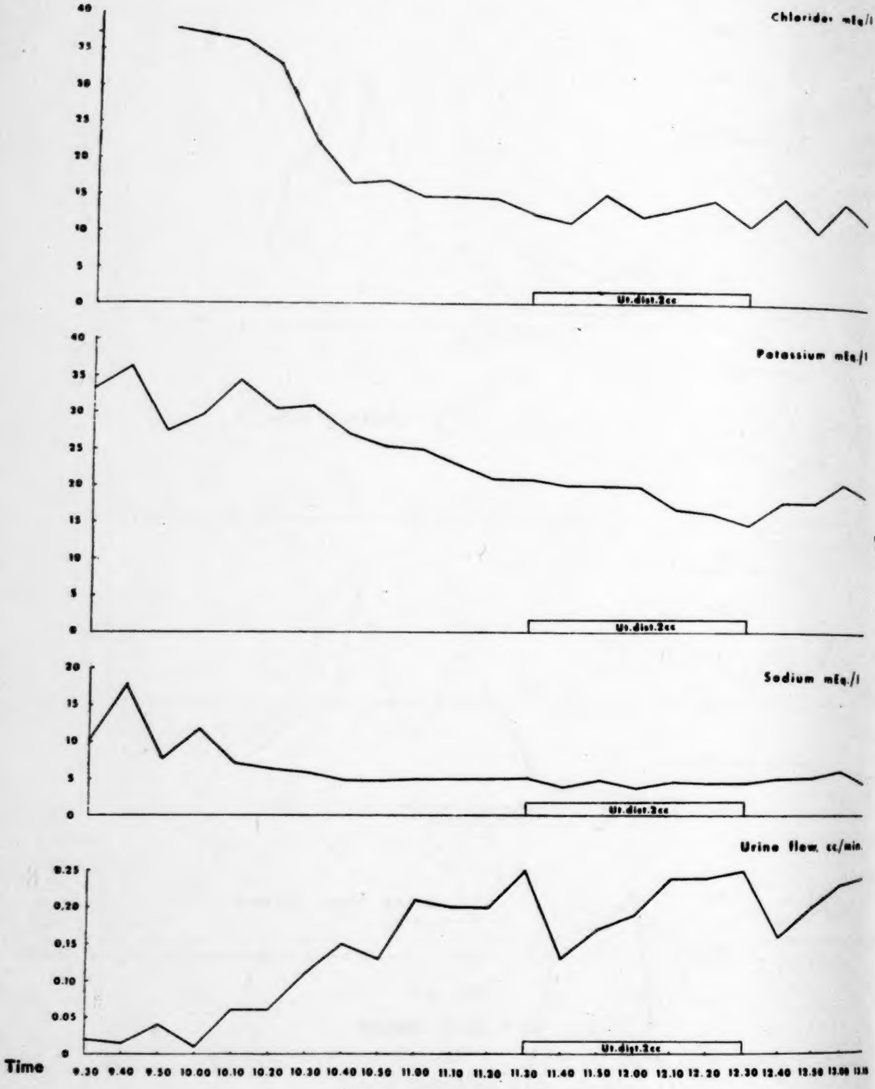

Fig. 19.

Rabbit VI 8. 11. 54

—— Both kidneys innervated, urine amount combined.

▭ Uterus distended 2 cc. 1 h.

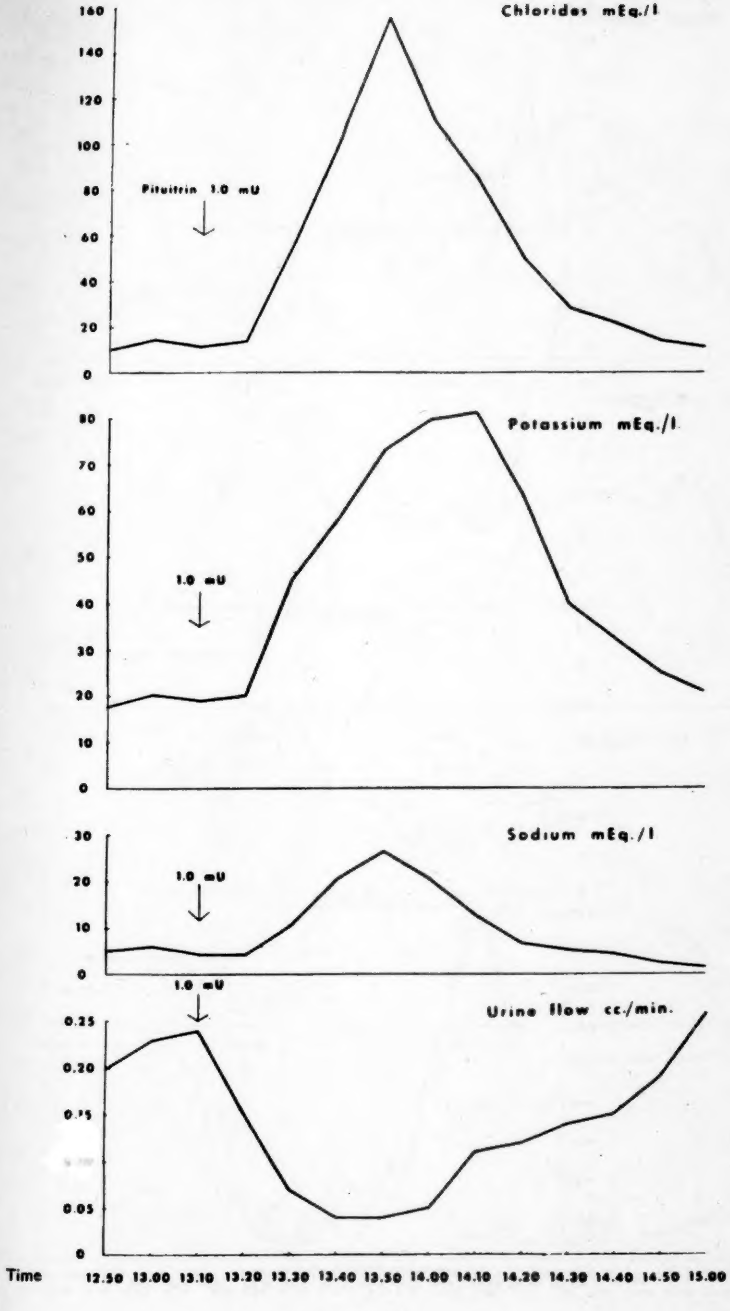

Fig. 20.

Rabbit V 25. 3. 55

——— Both kidneys innervated, urine amount combined.
At the arrows pituitrin 1.0 mU intravenously

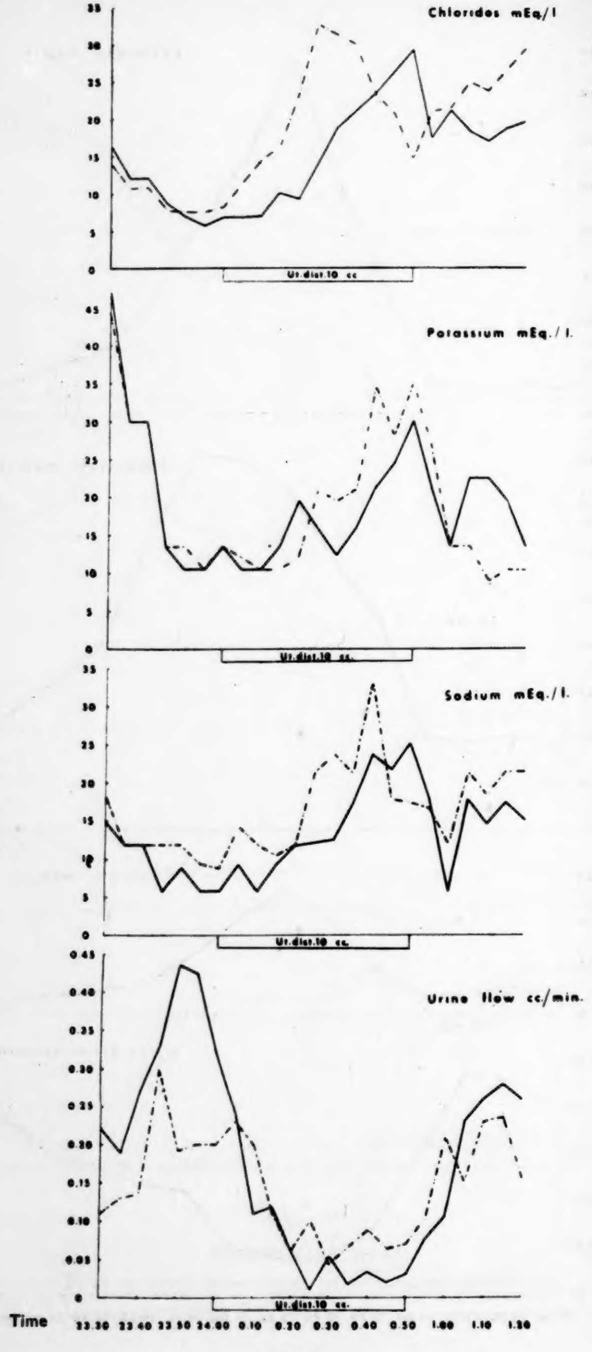

Fig. 21.

Rabbit X 12. 5. 55

-·-·-·- left, n. splanchnicus divided ——— right, innervated.

▭ Uterus distended 10 cc. 50 min.

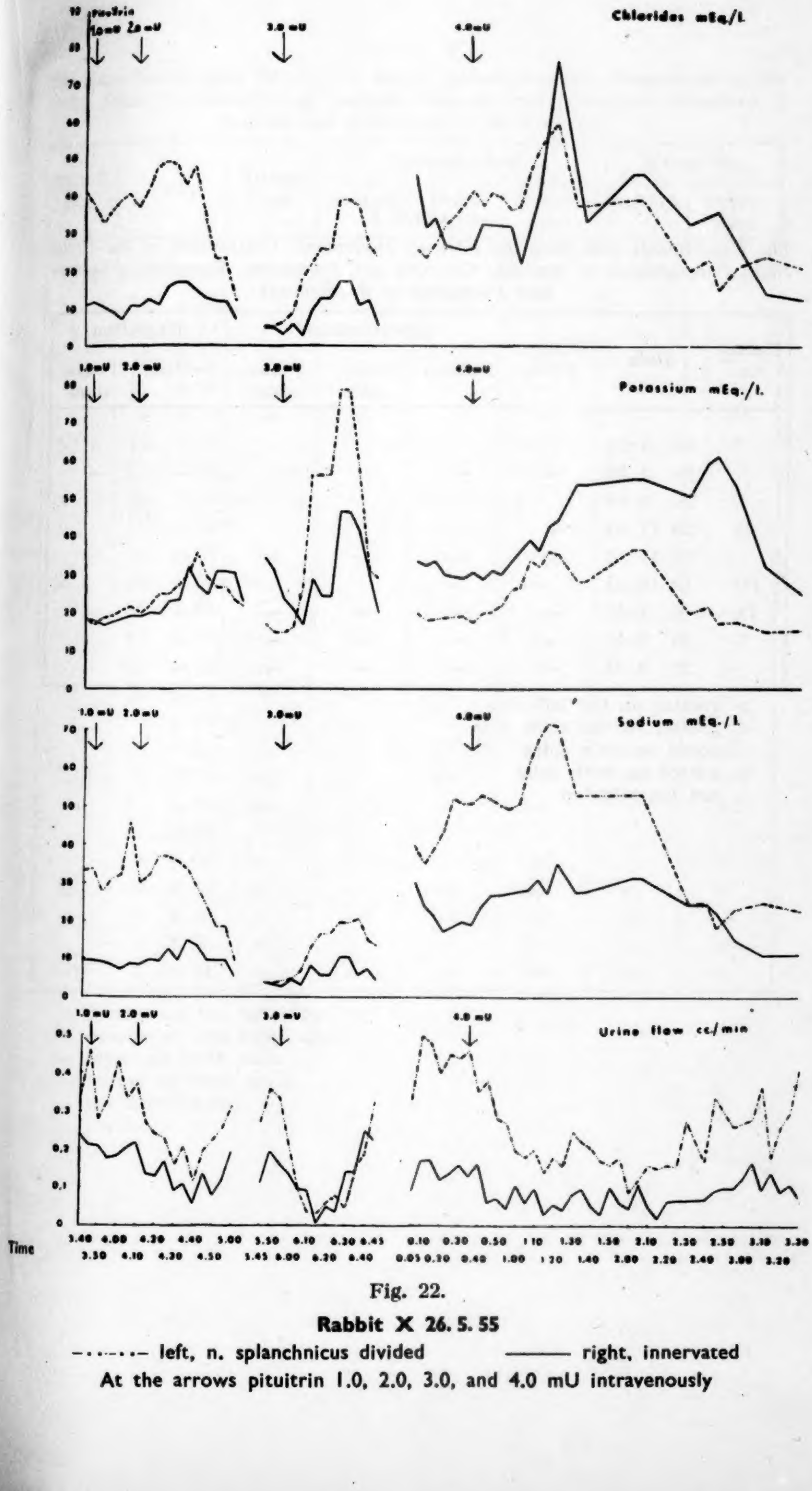

Fig. 22.

Rabbit X 26. 5. 55

-·-·-·- **left, n. splanchnicus divided** ——— **right, innervated**

At the arrows pituitrin 1.0, 2.0, 3.0, and 4.0 mU intravenously

TABLE 1

The Experiments with Both the Kidneys Innervated. Comparison of the Urine Flow, Concentration of Sodium, Chlorides and Potassium, Excretion of Sodium and Potassium of the Kidneys

Rabbit No.	Date	Urine Flow	Concentration			Excretion	
			Sodium	Chlorides	Potassium	Sodium	Potassium
I	18. 3. 55	<	>	>	>	<	<
	19. 3. 55	~	~	~	~	~	~
	26. 3. 55	<	>	>	>	<	<
II	20. 11. 54	~	..	..	..	..	..
	22. 11. 54	~	~	~	~	~	~
III	19. 12. 54	<	>	>	>	<	<
IV	6. 1. 55	~	~	~	~	~	~
V	20. 3. 55	~	~	~	~	~	~
	25. 3. 55	~	~	~	~	~	~

> greater on the left side
< greater on the right side
= equal on both sides
~ varied on both sides
.. not investigated

TABLE 2

The Experiments after Division of the n. splanchnicus sin. Comparison of the Urine Flow, Concentration of Sodium, Chlorides and Potassium, Excretion of Sodium and Potassium of the Kidneys

Rabbit No.	Date	Urine Flow	Concentration			Excretion	
			Sodium	Chlorides	Potassium	Sodium	Potassium
I	15. 4. 55	<	>	>	>	<	<
	17. 4. 55	<	>	>	>	<	<
VII	22. 9. 54	~	~	..	~	~	~
	25. 9. 54	~	~	..	~	~	~
	28. 9. 54	~	~	..	~	~	~
	9. 10. 54	=	=	..	=	=	=
VIII	12. 4. 54	~	~	..	~	~	~
	17. 4. 54	>	~	..	~	>	>
	27. 4. 54	>	~	..	~	~	~
	8. 5. 54	>	<	..	<	>	>
IX	26. 4. 54	~	~	..	~	~	~
X	30. 4. 55	~	~	~	~	~	~
	7. 5. 55	=	=	=	=	=	=
	12. 5. 55	~	~	~	~	~	~
	22. 5. 55	=	~	=	=	=	=
	26. 5. 55	~	~	~	~	~	~
	6. 6. 55	>	~	~	<	>	>
	20. 7. 55	~	~	~	~	~	~
XI	3. 5. 55	~	~	~	~	~	~
	16. 5. 55	~	~	~	~	~	~
	21. 5. 55	<	>	>	>	<	<
	3. 6. 55	~	<	<	=	~	~
XII	16. 2. 55	~	~	~	~	~	~
	23. 2. 55	=	=	=	=	=	=
	4. 3. 55	=	=	=	=	=	=
XIII	8. 10. 54	=	=	=	=	=	=

> greater on the left side
< greater on the right side
= equal on both sides
~ varied on both sides
.. not investigated

TABLE 3

Uterine Distension with Both the Kidneys Innervated. Change in Urine Flow and in the Excretion of Sodium and Potassium

Rabbit No.	Date	Uterine Distension		Urine Flow					Excretion of Sodium				Excretion of Potassium			
		Speed of Uterine Distension	Duration of Uterine Distension	Decrease of Urine Flow during Antidiuresis %		Assay of Antidiuresis (m U Pituitrin)	Urine Flow Increased in Relation to Uterine Distension (— after Cessation; ± at the Moment of Cessation; + Before Cessation)		Decrease of Sodium Excretion %		Sodium Excretion Increased (— after Cessation; ± at the Moment of Cessation; + Before Cessation)		Decrease of Potassium Excretion %		Potassium Excretion Increased (— after Cessation; ± at the Moment of Cessation; + Before Cessation)	
				Left	Right		Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
I	26. 3. 55	10 cc/45″	10′	100	88	..	—	—	100	88	—	—	100	89	—	—
II	24. 11. 54	3 cc/5′	30′	65		<0.25	+		66		+		65		+	
III	19. 12. 54	3 cc/1′	30′	100	61	0.5	±	+	100	90	+	+	100	86	±	+
IV	6. 1. 55	5 cc/5′	30′	↓ 55	66	..	+	+	*	*			13	31	+	+
V	20. 3. 55	10 cc/45″	25′	98	98	>1.0	—	—	92	89	+	+	86	96	+	+
	25. 3. 55	10 cc/45″	20′	42	18	<1.0	+	+	45	29	+	+	32	*	+	
	25. 3. 55	10 cc/45″	15′	40	78	<1.0	±	±	40	62	+	+	29	92	+	+
VI	27. 10. 54	3 cc/5′	1 ½h	99		1.0	+		73		+		87		+	
	8. 11. 54	2 cc/5′	1h	48		<0.5	+		56		+		50		+	
XIV	20. 4. 54	2 cc/1′	25′	65		..	±		10		+		*			
	20. 4. 54	2 cc/1′	20′	48		..	—		24		—		*			

↓ Temporary decrease of urine flow   * Excretion increased during uterine distension   .. not investigated

TABLE 4

TABLE 4

Uterine Distension after Division of the n. splanchnicus sin. Change in Urine Flow and in the Excretion of Sodium and Potassium

Rabbit No.	Date	Uterine Distension: Speed of Uterine Distension	Uterine Distension: Duration of Uterine Distension	Urine Flow: Decrease of Urine Flow during Antidiuresis % Left	Urine Flow: Decrease of Urine Flow during Antidiuresis % Right	Urine Flow: Assay of Antidiuresis (m U Pituitrin)	Urine Flow Increased in Relation to Uterine Distension (+ Before Cessation, ± at the Moment of Cessation, — after Cessation) Left	Urine Flow Increased in Relation to Uterine Distension Right	Excretion of Sodium: Decrease of Sodium Excretion % Left	Excretion of Sodium: Decrease of Sodium Excretion % Right	Sodium Excretion Increased (+ Before Cessation, ± at the Moment of Cessation, — after Cessation) Left	Sodium Excretion Increased Right	Excretion of Potassium: Decrease of Potassium Excretion % Left	Excretion of Potassium: Decrease of Potassium Excretion % Right	Potassium Excretion Increased (+ Before Cessation, ± at the Moment of Cessation, — after Cessation) Left	Potassium Excretion Increased Right
I	17. 4. 55	7 cc/1′	15′	75	86	0.5	+	—	85	68	+	+	88	53	+	—
	•17. 4. 55	10 cc/1′	25′	77	80	>0.5	+	+	50	56	+	±	83	72	+	+
X	30. 4. 55	3 cc/45″	20′	91	74	>3.0	—	—	50	54	+	+	92	92	±	±
	7. 5. 55	8.5cc/1′	40′	54	69	2.0	±	±	47	46	+	+	10	54	+	+
	12. 5. 55	10 cc/45″	50′	77	97	3.0	±	±	59	94	±	±	74	97	+	+
	26. 5. 55	9 cc/45″	70′	91	100	2.0	+	+	88	100	+	+	75	100	+	+
	6. 6. 55	4 cc/45″	35′	90	91	>3.0	±	—	85	77	±	—	68	90	+	±
XI	3. 5. 55	4 cc/45″	15′	50	93	>0.5	±	±	20	79	±	±	20	82	±	±
	16. 5. 55	10 cc/1′	1 h	100	70	>1.0	—	—	100	79	—	—	100	59	—	—
	21. 5. 55	10 cc/1′	2 h	100	100	>2.0	—	—	100	100	—	—	100	100	—	—
	3. 6. 55	5 cc/45″	10′	58	96	0.5	—	—	55	97	±	—	58	95	±	—
XII	16. 2. 55	8 cc/1′	20′	80	44	1.0	—	—	85	69	±	±	83	75	±	±
	23. 2. 55	8 cc/1′	20′	83	83	<1.0	—	—	45	33	—	—	72	81	—	—

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